TELEPHONE HUDSON 3-6126

Manufacturing Chemists' Association, Inc.

(FOUNDED 1872)

1825 CONNECTICUT AVENUE, N. W.
WASHINGTON, D. C. 20009

July 8, 1966

Dear Association Representative:

Subject: Proceedings of 94th Annual Meeting

We are sending you herewith copy of the Proceedings of the 94th Annual Meeting of the Association, held at The Greenbrier, White Sulphur Springs, West Virginia, on June 9-11, 1966. This contains a record of all business transacted at the meeting, as well as copies of reports and addresses presented.

A limited number of additional copies are available upon request.

Sincerely yours,

M. F. Cianz, Jr. (c)

Secretary-Treasurer

MFCJr/em
Enclosure

PROCEEDINGS

94th ANNUAL MEETING

of

Manufacturing Chemists' Association, Inc.

JUNE 9-11, 1966

THE GREENBRIER

WHITE SULPHUR SPRINGS, W. VA.

Houdry Process and Chemical Co., Division of Air Products and Chemicals, Inc.
- Blomquist, R. A.
- Burtis, T. A.
- Ferrell, F. M.
- Sidoroff, E. N.

I. C. I. (Organics) Inc.
- Cashford, William G. C.
- Reed, Firmin P.
- Richardson, Thomas
- Whitby, George F.

Imperial Oil Limited
- Doherty, T. B.
- Flanagan, J. W.
- Moreton, A. G.
- Wallar, R. E.

Interchemical Corporation
- Ault, Bromwell
- Hill, James T., Jr.
- Kress, Howard
- McDaniel, N. W.
- Porth, Victor J.

Interlake Steel Corporation
- Dye, W. A.
- Hayes, Scott B.
- Hoyt, Elton, III

International Minerals & Chemical Corporation
- Barber, Carl H.
- Batchelder, John E.
- Button, Bland B., Jr.
- Rudd, Thayer

Jefferson Chemical Company, Inc.
- Goerner, J. K.
- Griswold, D. L.
- Monaghan, P. R.
- Strawn, L. R.

The Journal of Commerce
- Wyss, Al

Kaiser Chemicals
- Davis, G. C.
- Sims, W. N.

Kay-Fries Chemicals, Inc.
- Vanderhoef, H. Kent

Koppers Company, Inc.
- Byrom, F. L.
- Eynon, D. L., Jr.
- Fritch, M. H.
- Jackson, W. B.
- Jones, J. D.
- Losch, E. D.
- Wheeley, B. O.

Eli Lilly and Company, Elanco Products Company Division
- Morton, Richard M.
- Orbaugh, William

The Lubrizol Corporation
- Clapp, Roger
- Eklund, C. W.
- Irwin, J. B.
- McGrew, M. M.

M&T Chemicals, Inc.
- Buchanan, H.
- Carpenter, C. H.
- Elf, J.
- Gloskey, C.
- Hirschland, H. E.
- Oberg, J. L.
- Zedler, R.

Mallinckrodt Chemical Works
- Anonsen, S. H.
- Fistere, J.
- Frese, D. J.
- Krause, J. H.
- Michener, W. F.
- Thayer, H. E.

Air Products

Date 4 June 1981

INTEROFFICE MEMORANDUM

Subject BUSINESS AND TRADE ASSOCIATION BUDGET 416

To E. J. Breyne — Corporate Financial Planning (Location, Organization, or Department)

From R. Domrzalski — Public Affairs (Location, Organization, or Department)

cc: W. J. Kendrick

Ed:

The following is a listing of the dues for various Business and Trade Associations which are to be budgeted to Ed Donley's organization code under account 416 for FY82.

I've listed what I believe will be the anticipated 1981-82 dues payment and the month in which it will be paid so you can plan accordingly.

Organization	Amount of Dues	Date Payable
Alliance for Free Enterprise	$25,000	May, 1981
American Council on Education	10,000	June, 1982
American Industrial Health Council	25,000	July, 1982
Business Council of Pa.	8,000	July, 1982
Chamber of Commerce (Penna.)	3,500	November, 1981
Chamber of Commerce (U. S.)	7,000	March, 1982
Chemical Manufacturers Assoc.	95,000	June, 1982
European Community - U. S. Businessmen's Council	3,100	November, 1981
Industrial Development Corp. of Lehigh Valley	1,200	July, 1982
National Minority Supplier Development Corporation	3,000	January, 1982
TOTAL	$180,800	

RD:amr

(320)

AP00037461

MANUFACTURING CHEMISTS ASSOCIATION

DESCRIPTION:

Founded in 1872, MCA is the prime trade association representing the U.S. Chemical Industry. It operates through 10 technical and functional committees and their task-oriented subgroups which are staffed by MCA personnel and in which the relevant company experts from many of the 190 MCA members participate. Lobbying is carried out under the direction of MCA's Director of Government Relations, Bill Stover, and its Government Relations Committee. The President of MCA, Bob Roland, was recently brought on board to fulfill the desire of top Chemical Industry executives to beef-up the trade group's image and active involvement in Washington affairs.

KEY UNIT(S):

Board of Directors - 32 members serving for 3 year terms with 1/3 turnover each year. Supervision over MCA's activities is primarily exercised by the Board's Executive, Finance, and Program Committees.

New Board members are selected each May by the Chairman of the Board and Executive Committee together with MCA's President. An outgoing Board member cannot succeed himself for at least a year, but another Executive from the same company can be appointed in the interim.

AIR PRODUCTS PRESENT INVOLVEMENT:

Ed Donley is presently serving as Chairman of MCA's Board through 31May 1979. Numerous Air Products employees, especially from the Chemicals Group, actively participate in MCA's committees. Annual Air Products' dues for 1978 were $45,000 and will increase in 1979.

VALUE OF SERVICE:

MCA is probably the most relevant of the various trade groups to which Air Products belongs since its legislative and regulatory efforts closely parallel Chemical Group interests and concerns. Close coordination and participation in MCA's legal, technical, and government relations activities can immeasurably enhance Air Products individual efforts. Board involvement provides an excellent opportunity to interact with the top Executives of the Chemical Industry. (see list attached).

ADDED RESPONSIBILITIES:

MCA's Board meets 5 times a year (5 days). Service in a leadership position of course involves additional time.

RECOMMENDATION:

Although Ed Donley's term as Board Chairman and member would normally expire on 31 May, 1979, Bob Roland has indicated that he would like Ed to stay on the Board for an additional period as a Board member to provide advice on the reorganization initiated during Ed's tenure as Chairman.

INDUSTRIAL TOXICOLOGY

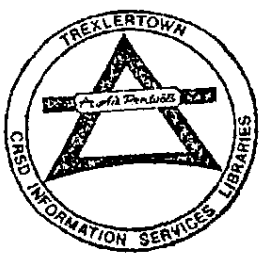
THIRD EDITION

Alice Hamilton, M.D.

Late Assistant Professor Emerita of Industrial Medicine,
Harvard School of Public Health, Boston, Massachusetts

Harriet L. Hardy, M.D., F.A.C.P.

Clinical Professor of Occupational Medicine, Department of Preventive Medicine, Harvard Medical School, Boston, Massachusetts
Board of Consultation, Massachusetts General Hospital, Boston, Massachusetts
Former Assistant Medical Director in charge of Occupational Medical Service, Massachusetts Institute of Technology, Cambridge, Massachusetts
Visiting Professor of Medicine, Dartmouth Medical School, Hanover, New Hampshire



PUBLISHING SCIENCES GROUP, INC.
Acton, Massachusetts
a subsidiary of CHC Corporation

with the assistance of

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Printed in the United States of America.

International Standard Book Number: 0-88416-029-7

Library of Congress Catalog Card Number: 73-91922

PREFACE

It was the privilege of HLH to serve as junior in the preparation of Dr. Alice Hamilton's volume, *Industrial Toxicology*, for its second edition in 1949. The intention of this third volume is to help practitioners and to attract medical students and physicians in the field of occupational disease by combining Dr. Hamilton's pioneer wisdom with current industrial hygiene practice and the authors' clinical experience as internists especially interested in industrial illness. To include every reported occupational insult and the reaction to it would make this book unwieldy. This volume does not attempt to include a description of every industrial operation and of each use of a potentially hazardous material. Aside from the problem of size of such an undertaking, it is a fact that, during the period this book is being printed, technical innovations will be introduced that may result in new hazards to workers. The plan, therefore, has been that this edition serve both a ready reference and a point of view toward job-related disease as etiology, an often neglected possibility. Attention is drawn to Section One, designed to be of practical value in guiding the clinician to the criteria needed for a correct diagnosis of occupational disease. Practical advice is included on the difficult demands of the United States Workmen's Compensation benefits, a subject many physicians avoid.

The updating of certain sections of the 1949 edition of *Industrial Toxicology* has required considerable reworking. Updating and revision with needed additions have been developed by me and my colleagues Drs. Asher Finkel, Clarence Maloof, John Stoeckle, and Lloyd Tepper. This edition has been enlarged by new sections dealing with potential risks from exposure to plastics and pesticides, occupational causes of pulmonary disease, and biologic hazards to workers of importance to the physician. The section on radiant energy includes the great advances in knowledge since 1949 with emphasis on facts of importance to physicians. Edwin D. Flack prepared the chapters on lasers and microwave radiation and updated those on ultraviolet and infrared radiations.

The attempt has been made to provide the reader with a practical, workable bibliography. To accomplish this, the decision has been made to refer, with rare exceptions, to only literature published and available in English. Much of importance in the field of occupational medicine has appeared in other languages, especially that knowledge that predates World War II. By using reference to abstracts, however, and by citing data in earlier editions of

this book and current texts, it is hoped that errors of omission are few. In addition, appendixes have been added, which list both sources of detailed discussions and subjects in the field of occupational medicine not covered in this book. References to animal toxicity studies have been deliberately restricted to those of unusual interest to students of worker illness. HLH decided to omit most trade names of industrially used materials except for those that are almost a part of daily language, for example, in the United States, nylon and teflon.

The final draft has been strengthened by careful reading for errors and omissions by my Massachusetts Institute of Technology colleagues, members of the staff of the Occupational Medicine Service, Richard Chamberlin, George Boylen, Joseph Leahy, Stephen Piccolo, and Samuel Levin. Gratitude is due Dr. Margot Becklake of the Royal Victoria Hospital of Montreal who reviewed the sections dealing with occupational hazards to the lung. I have had unusual counsel and help from colleagues abroad: the late Dr. Andrew Meiklejohn, Dr. Archie Cochrane, Dr. John Gilson, Dr. Katharine Williams, Dr. Richard Schilling, and Dr. Luigi Parmeggiani. Dr. A. O. Seeler and Dr. Thomas Almy, by freeing me from my usual rounds, made this work possible. The original stimulus for this work came from my colleague, the late Dr. J. Howard Means, Chief of Medicine, and my surgical coworker, Dr. J. Gordon Scannell, both of the Mass. General Hospital, Boston, Mass.

The preparation of the manuscript was begun by the late Harriet Newcomb. Miss Jeannine Vallee and Frances Guiggio carried out the difficult preparation of a workable draft. Finally, the book depended for completion on the good will of Miss Elizabeth O'Brien, Mrs. Jean Lawe, the competence and energy of Mrs. Catherine Johnson, Mrs. Abby McLaughlin, and Mrs. Patricia Davis. I must also record my gratitude for the loyal support of Miss Alice Kennedy and the tireless encouragement of my sister, Mrs. J. Hardy Stewart.

Lincoln, Massachusetts
December 1973

Harriet L. Hardy, M.D.

SECTION FOUR

CHEMICAL COMPOUNDS II

ALIPHATIC HYDROCARBONS • 1

The aliphatic series of hydrocarbons includes the saturated (paraffin, methane, or alkane) and the unsaturated (olefin, ethylene, or alkene) compounds, which are derived almost exclusively from petroleum or petroleum processing.

SATURATED ALIPHATIC HYDROCARBONS

The saturated aliphatic series is comprised of gases (methane, ethane, propane, and butanes), liquids from pentanes (C_5) through C_{16} compounds, and solids. Compounds in the series are used as fuels, solvents, and lubricants, most commonly as mixtures. From the toxicological point of view these compounds are not particularly active. The first two members of the series, methane and ethane, have no known biological properties and exert an effect only as simple oxygen-replacing asphyxiants. Methane, as the principal constituent of natural gas, is widely used as a domestic fuel. As such, it is biologically inert and stands in marked contrast to the toxic carbon monoxide-containing manufactured gases (water gas and producer gas) which were in common use prior to the transcontinental transportation of natural gas from petroleum-producing fields to commercial markets. The concept of toxic domestic fuel gas remains sufficiently prominent in American thinking to cause a number of attempts at suicide each year by persons who "take gas." The normal consequence of this attempt is an explosion rather than intoxication. The lower limit of flammability for methane approximates 5 percent. In the mining industry methane may be known as marsh gas or fire damp, the principal cause of explosions in coal mines. This gas may become a simple asphyxiant in poorly ventilated pockets in coal mines into which the gas may rise because of its low density.

From time to time one notes clinical reports in the medical literature referring to a "gas leak syndrome" (Sherman and Harris, 1968). The usual history includes an upper respiratory infection or other mild illness which requires that a patient be confined in a room containing a gas heater. Complaints of headache, weakness, myalgia, ataxia, and light-headedness or fainting appear to be associated with confinement and unrelated to the primary illness. The physical and laboratory examinations are noncontributory. There is no evidence that leaking natural gas has produced these clinical complaints. It is more than likely that whatever symptoms are related to the heating system are in fact related to faulty flues, causing leakage of carbon monoxide. Insufficient supply of air to replace that which is consumed by the heating system may result in negative pressure which causes back drafts from flues.

In general the saturated hydrocarbons from propane (C_3) through the octanes (C_8) show increasingly strong narcotic properties. Heavier members of the series become insufficiently volatile to produce narcotizing concentrations in air unless heat is applied or vapor-saturated atmospheres are encountered in tanks or other confined spaces. The margin between narcosis and lethal depression of vital centers is too narrow to permit these compounds to be used as surgical anesthetics. Narcotic effects may be accompanied by exhilaration, dizziness, and headache. There may also be a loss of appetite, nausea, a persisting taste of gasoline, confusion, inability to do fine work, and loss of consciousness in extreme cases. Removal from exposure usually results in a rapid clearing of symptoms, although there may be a transient exacerbation upon coming into the open air.

risks to exposed workers

The vapors of compounds from pentane through octane are increasingly irritating to mucous membranes, although none of these materials are actually strong irritants. The liquids, as fat solvents, extract sebum from the skin leaving a dry irritated surface prone to cracking and bacterial infection. The likelihood of exposure to individual members of this series is very small; most commonly exposures are to mixtures which may be variously termed petroleum ether, benzine (not benzene), petroleum naphtha, gasoline, mineral spirits, so-called Stoddard solvent, and varsol. Higher boiling mixtures appear as kerosine or jet fuels; heavier yet are the lubricating oils. Such mixtures may contain various branched and cyclic compounds such as benzene which have important toxicological properties of much greater significance than those of the quantitatively predominant aliphatics. The composition of these mixtures will invariably reflect the origin of the petroleum, molecular modifications effected at the refineries, seasonal fuel requirements, specifications by users, and the addition of highly dissimilar materials such as antioxidants, anti-knock compounds, corrosion inhibitors, combustion improvers, and dyes.

From the practical point of view, and in the absence of benzene, the manifestations of exposure to vapors of these hydrocarbon mixes are those typical of exposure to heptane or octane—viz., giddiness, vertigo, headache, and anesthetic stupor. In massive acute exposures, as may be experienced upon entry into gasoline storage tanks, rapid central nervous system depression may occur with sudden collapse, deep coma, and death. There may be convulsions indicative of brain irritation or apneic anoxia. Full recovery without sequelae is the rule. However cerebral microhemorrhages or focal

post-inflammatory scarring have been suggested as the etiology of epileptiform seizures months after the acute episode. Pathological examination of tissues from fatal cases gives evidence for widespread microhemorrhagic phenomena. Irritation of the upper and lower respiratory tract and visceral damage has also been described. From time to time cases are reported of sudden death in persons who have inhaled vapors of volatile liquids such as gasoline. Usually this exposure is not in the line of work but reflects an attempt to obtain an exhilarating or similar psychopharmacological experience ("jag"). The best evidence is that these deaths are due to fatal cardiac arrhythmias in which endogenous releases of epinephrine are implicated (Reinhardt et al., 1971). There is no convincing evidence that prolonged exposures to vapors of aliphatic hydrocarbons, as in the case of gasoline station attendants, can cause harmful effects.

These solvent mixes are all primary irritants and defatting agents when applied to the skin. Carcinoma of the skin which has followed prolonged dermal exposure to cutting oils almost certainly represents a reaction to specific carcinogenic polycyclic aromatic compounds and not to the aliphatic materials which are the predominant constitutents.

In industrial situations kerosine and lubricating oils are insufficiently volatile to cause respiratory tract damage. These materials can enter the lungs upon aspiration following ingestion and spontaneous or induced vomiting. Gerarde (1963) has shown experimentally that the ingestion of these mixes is not especially injurious in the absence of vomiting. When vomiting occurs, however, hydrocarbon mixtures of low viscosity (e.g., gasoline) are readily aspirated into the lungs. In such cases there may be rapid death from cardiac arrest, asphyxia, or respiratory paralysis. Rapid systemic absorption may lead to central nervous system manifestations such as convulsions. The aspiration of lesser quantities or of somewhat heavier molecular-weight compounds (C_{10}–C_{15}) such as kerosine results in a slower progression of events, marked by chemical pneumonitis with prominent endothelial damage and pulmonary hemorrhage and edema. Heavier and more viscous materials such as mineral oil and motor oil are not readily aspirated. The pulmonary reaction to these high-viscosity hydrocarbons is one of "lipoid-pneumonia," a chronic localized tissue response, as has been observed in persons taking mineral oil-based nose drops over the course of years.

Clinical experience with hydrocarbon ingestion, especially of kerosine by children, is consistent with these observations (Baldachin and Melmed, 1964). The most common clinical and

pathological observation is chemical pneumonitis with pulmonary hemorrhage and edema and complicating bacterial pneumonia. Central nervous symptoms are related to systemic absorption of particularly the lighter molecules, and depression or coma are common. When hydrocarbons have been accidentally ingested, the prevention of aspiration is of the utmost importance. The advisability of gastric lavage is a debatable point (Press, 1962), but best current practice seems to indicate this step if precautions are taken—namely, intratracheal intubation.

LUBRICATING OILS

Lubricating oils are based upon aliphatic hydrocarbon molecules containing seventeen or more carbon atoms. Such oils are complex mixtures containing, as well, small amounts of aromatic and polycyclic substances and a broad variety of dissimilar materials known collectively as "additives." The functions of these additives are multiple; they may inhibit corrosion or oxidation, preserve film integrity, alter viscosity, suppress bacterial growth, and act as detergents. Some of these materials have biological properties which may cause lubricating oil to have health significance in excess of that related to simple aliphatic compounds. A number of skin reactions to these additives to petroleum oils are described in texts on occupational dermatology. Problems are not common, however, and affect primarily those individuals who have developed a high degree of hypersensitivity.

CUTTING OILS

Cutting fluids are for the most part dissimilar in composition to the lubricating oils. Cutting fluids are applied to metal-cutting tools to facilitate and accelerate machining operations, to cool cutting surfaces, and to carry metal chips away from work surfaces. It is believed that cutting fluids are the most common cause of industrial dermatitis and, as such, represent a major cause of disability, lost work time, and work restriction. The problem is exacerbated by the fact that large volumes of fluid may be used at each machine, that compressed air used in chip removal may spatter fluids over the operator and his clothing, and that sharp metal chips imbedded in rags and clothing or on the skin cause small lacerations which impair the skin's resistance to irritating compounds and infection. Cutting fluids can be classified into three categories: (1) insoluble oils, (2) soluble fluids, and (3) synthetic fluids. Insoluble oils are based upon petroleum oils to which are added various animal or vegetable oils, fats, and waxes. These oils are commonly recirculated for long periods, with metal chips removed by filtration, and are used chiefly in heavy machining

operations such as in the cutting of engine blocks. Soluble fluids or oils are based upon an emulsion of oils and water and are milky in appearance. The chemical or synthetic fluids are mostly water with small amounts of wetting agents. To the basic fluid, regardless of type, various materials may be introduced to provide or improve specific desirable properties. These additives include germicides such as formalin, mercurials, phenolic compounds; emulsifiers such as soaps, petroleum sulfonates; corrosion inhibitors such as borates, dichromates, amines; and extreme pressure compounds of sulfur, chlorine, or phosphorus. The oil-water emulsions tend to become rancid, but they are good coolants, economical, and non-combustible.

toxicity

The prevalence of cutting fluid dermatitis is related to the hygienic status of the working place and the worker. Poor machine enclosure, the use of degraded and contaminated fluid, inadequate washing facilities for personnel, and an insufficient supply of clean clothes and protective garments contribute to the problem. Machinists who are prone to acne-seborrhea or who are swarthy and hirsute are relatively susceptible to blockage of hair follicles by insoluble oils and the consequent folliculitis. Individuals with a previously unresolved skin problem or dry or atrophic skin are vulnerable to soluble fluids, especially those which are clearly alkaline or which contain wetting agents.

The usual cutaneous response to oil-based materials is an oil folliculitis which arises as a result of chemical irritation and mechanical plugging of the follicular canal. Onset of the problem usually occurs soon after the first exposure and is marked by acute reactions starting on the dorsal surfaces of the hands and fingers, the extensor surfaces of the forearms and thighs, and the abdomen (i.e., those surfaces which are in contact with oil or oil-soaked clothing). Comedones and perifollicular papules and pustules ("oil boils") are present. Melanosis may develop later. Secondary infection may occur, but bacteria in the oil are rarely primary skin pathogens and are rarely the single cause of folliculitis. Clinical manifestations clear rapidly with the termination of exposure and do not resolve if the exposure is continued. Exposure is controlled through proper machine design to prevent spattering, clean clothing, protective garments, and careful attention to handwashing.

Certain petroleum oils have carcinogenic constituents; this is especially the case with shale oils, which are manufactured and used outside the United States. There are no good data to establish the prevalence of skin cancers among machinists in this country,

but malignant tumors or precancerous keratoses are not known to occur in significant numbers above those that occur in a control population. The carcinogenic potency of specific oils has nothing to do with their ability or lack of ability to produce dermatitis. Knowledge of occupational malignancy of the skin has a long and important history dating from 1775 when Pott identified scrotal cancer in English chimney sweeps (Merewether, 1956, pp. 304–361).

The skin reaction to emulsion and synthetic fluids is variable and may include maceration, dryness and "chapping," reddening, and vesiculation. These fluids are potent defatting agents. Bacterial growths in the fluid do not appear to be directly injurious to workers, but rancid fluids and products of bacterial action can be the etiology of skin disorders. As is the case with insoluble oils, both treatment and prevention are based on the control of exposure. Corticosteroid creams may be used as an adjunct in the treatment. The value of "barrier" creams is not unanimously accepted, but they do offer modest usefulness in certain situations.

Individual additives in cutting fluids can be a cause of either primary irritative or hypersensitive dermatitis. Detergents, soaps, and wetting agents defat the skin, and alkaline materials damage the keratin of protective superficial skin layers. Formalin in germicides is a sensitizer. Additives containing sulfur and chlorine are direct irritants, although so-called chloracne is not associated with cutting fluids. Nickel or chromates derived from metals being cut can be a source of allergic dermatitis. Harsh abrasive soaps and solvents such as gasoline and kerosine may contribute to chemical and traumatic dermatitis since these cleaning materials are common in machine shops. While grime and grease can certainly be removed from the skin with these substances, it is safer to utilize less injurious cleansers commercially available.

The evidence indicates that exposures to mist sprays of insoluble oils used in machine operations are not harmful to the respiratory tract.

UNSATURATED ALIPHATIC HYDROCARBONS

In general the unsaturated aliphatic hydrocarbons lack biological properties which are important to occupational medicine. These hydrocarbons are for the most part products of the petrochemical industry and are formed in the cracking and dehydrogenation of petroleum fractions. These compounds are essential to the synthesis of various plastics and synthetic rubbers. Ethylene and propylene are weak anesthetics at high concentrations and have been used in surgical procedures. The butylenes, butadiene, and isoprene (C_5) have similar properties. Acetylene is also an anesthetic material with no known injurious effects upon

man. When acetylene is prepared from the addition of water to calcium carbide, phosphine (PH_3) may be generated from phosphides in the impure carbide. Hence phosphine may be a significant contaminant of commercial grades of acetylene. The wide range of flammability of this gas and its tendency to form explosive acetylides with metals warrant special attention.

AROMATIC HYDROCARBONS • 2

The aromatic series of compounds is based upon benzene and molecules which incorporate one or more benzene rings. Many of the most common members of the series were obtained initially from the distillation of coal in the coking process. The industrial demand for benzene regularly exceeded the supply available from coal carbonization by the early 1950s, and an increasing proportion of the aromatic chemicals is now derived from the reforming or dealkylation of petroleum-derived materials. At the present time the petrochemical industry provides the major source of aromatic compounds. Both coal- and petroleum-derived aromatics are produced in ways which lead to complicated mixtures of many compounds in the series. Accordingly crude distillates and unpurified commercial products may contain substances not indicated on the label, which often reflects only the principal constituents. Minor constituents in industrial or technical grade solvents distributed without adequate warning have been, however, important causes of toxic reactions.

BENZENE

Benzene, the parent member of the series, has been the most significant from the toxicological point of view. In many instances of intoxication the compound responsible for disease has not been identified as benzene since hazardous amounts of this compound have been present in technical grade "toluene" or other solvent mixes. The European practice of using crude benzene to improve the anti-knock properties of gasolines was utilized in the United States until about 1950 and led to cases of benzene intoxication in persons using this blended motor fuel for solvent purposes.

A lack of precision in terminology is a serious problem in recognizing benzene hazards. There has been confusion with the term benzine, which denotes a low-boiling petroleum fraction of predominantly aliphatic compounds and is similar to ordinary gasoline. Benzine, if uncontaminated by benzene, does not have the hematopoietic effect characteristic of chronic benzene poisoning. The term benzol, gradually losing in popularity, has usually been associated with crude aromatic mixtures, predominantly benzene. In cases of suspected benzene poisoning or when effective health conservation measures are to be applied, it is urgent to learn, by chemical analysis if necessary, whether or not benzene is present and, if so, in what concentration. Since usage in industry varies at different periods as a result of cost and technical needs, it can be necessary to repeat an assay for benzene at intervals. Al-

though benzene remains an important solvent, over 90 percent of benzene production goes into the synthesis of other organic compounds. Benzene is the primary raw material for styrene used in synthetic rubber, for phenol, for nylon intermediates, and for synthetic detergents of the alkylauryl sulfonate type. Solvent benzene used in rubber cements and in paint strippers has been a frequent cause of injury inasmuch as these materials have often been used under hazardous circumstances by people unaware of the presence or properties of this compound. Benzene used in laboratory extractions and in chromatographic separations is often used under hazardous conditions.

toxic effects

Like most organic solvents, benzene is a central nervous system depressant at high concentrations and may cause acute narcotic reactions. These are nonspecific and may extend from mild manifestations such as lightheadedness, headache, and excitement to respiratory paralysis and death with or without convulsions. A pattern of apparent drunken behavior due to benzene has been called "benzol jag" by industrial workers and consists of euphoria, unsteady gait, and confusion. Recovery from acute benzene narcosis is complete unless the levels and duration of exposure cause pathologic changes.

Chronic benzene poisoning is of far greater toxicological significance. Its incidence has been gradually decreasing over recent years with the improvement of industrial hygiene measures and a thoughtful and effective search for technically satisfactory and less toxic benzene substitutes. The intoxication is characterized primarily by a disturbance of the hematopoietic system which can affect every cell line. The clinical picture may vary from person to person. It is often not possible to establish a firm relationship between character of the benzene exposure and the disease. The view that women are more susceptible than men and that the young are more vulnerable than older persons is traditional but not well supported by sound epidemiological data. It is probable that the anemia characteristic of women due to the demands on bone marrow of menses and pregnancy makes them more vulnerable to benzene. In most cases chronic benzene poisoning has followed repeated exposures to unsafe air levels of benzene vapor over the course of months or years.

Clinical manifestations of chronic benzene poisoning tend to be insidious in onset, and most recorded cases have been well advanced at the time of diagnosis (Hunter, 1939; Mallory et al., 1939). Classical signs of major hematopoietic injury such as purpura and overwhelming agranulocytosis are rarely noted in the

more recent literature, however. The more common initial findings tend to be nonspecific and include fatigue and loss of appetite. Hematological evaluation may show anemia, leukopenia, and thrombocytopenia; however, all three cell lines are not always affected or affected to the same degree. Immature cells may be found in the peripheral blood, and there may be an eosinophilia or leukocytosis. The bone marrow may be hypoplastic, hyperplastic, or relatively unchanged. These observations do not correlate well with the clinical picture, the character of the exposure, or the prognosis. In some workers with chronic benzene poisoning there is evidence for shortened red cell survival or extramedullary hematopoiesis. From the clinical point of view, idiopathic aplastic anemia and bone marrow failure due to benzene cannot be distinguished.

While there has been no doubt for many years that benzene can produce fatal aplastic anemia, the association between benzene exposure and leukemia has been a matter of more recent controversy. It is now generally accepted that benzene can produce leukemia of varying forms and that such leukemia can appear with or without an antecedent history of aplastic anemia (Vigliani and Saita, 1964). The conversion of aplastic anemia to leukemia is not uncommon in cases in which the cause of the anemia is unknown. Chronic myelogenous leukemia appears to be the most common type associated with benzene exposures, but acute myelogenous and acute and chronic lymphocytic varieties have been reported as well. Erythroleukemia (Di Guglielmo's disease) with prominent proliferation of the erythroblastic elements of the marrow has also been associated with benzene exposure (Rozman et al., 1968).

Interest in lymphocyte cultures and chromosomal patterns over the past decade has led to their use in epidemiological studies of chromosomal aberrations in benzene-exposed individuals (Tough and Court Brown, 1965; Forni, et al, 1971a, 1971b). It has been possible to demonstrate abnormal chromosomal patterns, in comparison with controls, among former benzene workers with no exposure for over two years. This approach may ultimately shed light upon the nature of the long latent periods which have been described in persons without exposure for many years but who eventually develop aplastic anemia or leukemia.

While it is difficult in a single given case to be sure that current anemia or leukemia is the result of benzene exposure twenty or thirty years ago rather than a "spontaneous" event, there are enough such cases to present convincing evidence of a causal association (Medical Grand Rounds, 1950; DeGowin, 1963). It is also worth mentioning that in a number of these cases the initial

exposures to benzene were complicated by exposures to other substances (e.g., chlorinated hydrocarbons) which might possibly have had a synergistic effect in producing whatever altered reactions are necessary for this clinical course (Medical Grand Rounds, 1950). The mechanisms for this interpretation of events are not known.

therapy and control

Therapy for chronic benzene poisoning, when manifested either as aplastic anemia or leukemia, is that which is used when these diseases occur without known cause.

The prevention of acute and chronic benzene poisoning is based on control of levels of benzene in air. Convenient survey detector tube and physical instruments are available for measuring benzene in ambient atmospheres. The threshold limit value for benzene has dropped repeatedly in the last several decades, and a concentration of 25 ppm is now considered acceptable for eight-hour exposures at the work place. Evidence of hematopoietic injury at previously higher working levels has led to present criteria (Medical Grand Rounds, 1950). It is also possible to measure metabolites of benzene in the urine of workers and thereby establish an index of exposure. The urinary sulfate ratio has been used for years to express that portion of urinary sulfate which is present in ionic form, normally at least 80 percent (Elkins, 1959). In benzene exposure, the excretion of phenol sulfate increases so that the proportion of inorganic sulfate drops to less than 80 percent. Inorganic sulfate ratios of less than 80 percent are considered indicative of excessive exposure. Other organic sulfates of nonoccupational origin may be related to the ingestion of bananas, smoked meats or fish, or phenolic drugs. Phenol concentrations in the urine can also be determined, the normal range being 20 to 30 mg/L (Doctor and Zielhuis, 1967). An eight-hour exposure to benzene at an air concentration of 30 ppm will result in a urinary phenol level of about 150 to 200 mg/L.

TOLUENE AND XYLENE

Toluene (also called methyl benzene and toluol) and the xylenes (dimethyl benzenes, xylol) have, relative to benzene, much lower toxicity and volatility. Nevertheless, these compounds, though predominant in certain industrial solvent mixtures, may be associated with benzene to a degree which has been responsible for benzene-induced injury to the hematopoietic system. Those persons responsible for the safety of the work environment must be sure that so-called toluene or xylene is free of significant amounts of benzene. Various technical solvent mixes such as "solvent naphtha" or "Hi-flash naphtha" may not be aliphatic naphtha at all but may be blends of toluene, xylenes, and heavier related compounds.

References in the literature to bone marrow failure caused by toluene have created confusion with respect to the toxic properties of this compound. An examination of these reports suggests that much of such "toluene" toxicity as had been observed was in fact due to the presence of benzene in a solvent mixture derived from coal tar distillation. In other situations aplastic anemias occurred even though benzene-free toluene was used. Here a careful reading of the case histories generally discloses prior exposure to benzene. The action of benzene may not become apparent for years after the cessation of exposure, and subsequent exposure to toluene need not influence the toxic process, the basis for which had already been established.

Animal studies of toluene toxicity have failed to demonstrate a convincing myelotoxic effect. Von Oettingen, Neal, and Donahue (1942) tested the effect of fumes of toluene on three normal persons, subjecting them to concentrations from 50 ppm up to 800 ppm for daily periods up to eight hours. No definite changes were found in the white blood cell picture, in the circulation, or in the respiration by exposure even to the highest concentration of toluene. At 200 ppm there was a slight, but definite, impairment of coordination and reaction time, which might bring about a greater liability to accident. With concentrations over 200 ppm these effects become increasingly severe, and at 600 to 800 ppm three hours' exposure resulted in severe fatigue, extreme nausea, confusion, lack of self-control, incoordination, and staggering galt. Since evidence of neurological impairment occurs at a toluene concentration of 200 ppm, the continuing utilization of this value as the threshold limit value has been questioned, and a reduction to 100 ppm has been proposed.

While the preponderant evidence is that chronic exposure to toluene does not produce injury to the bone marrow, isolated cases of this clinical picture and a history of toluene exposure exist. Gattner and May (1963) reported the case of a sixteen-year-old boy who was exposed over the course of nine months to high concentrations of benzene-free toluene used in the cleaning of printing presses. He came under medical care because of fatigue, weakness, and dizziness and was found in the course of his clinical evaluation to have leukocyte counts as low as 1,400 cells/mm^3 with a platelet count of 63,000 cells/mm^3. Although a clear causal association cannot be established in this situation, the evidence associating toluene with myelotoxic changes cannot be ignored.

The effects of toluene on the central nervous system, viz., dizziness, weakness, confusion, are not specific for this compound and are typical of the responses to hydrocarbon solvents. The euphoric phase of anesthesia, a manifestation of toluene toxicity, is

attractive to certain individuals who have made a practice of "glue sniffing." Sudden death among "sniffers" may be attributed to lethal cardiac arrhythmias following "sensitization" of the myocardium (Reinhardt et al., 1971). In experimental situations benzene has been found to be very potent in this respect, and it is reasonable to anticipate similar effects from toluene.

control

Toluene does not cause a reduction in the ratio of inorganic sulfates excreted in the urine. Toluene does cause an increased excretion of hippuric acid which can be used to evaluate toluene exposures. The hygienic status of the working place is determined by the direct measurement of toluene in the atmosphere.

Toluene is irritating to the skin and conjunctival membranes. The vapors at high concentrations are irritating to the respiratory tract. The xylenes are very similar to toluene in their toxic effect.

DIPHENYL AND DIPHENYL OXIDE

Diphenyl and diphenyl oxide are used in industry primarily as heat transfer media. Diphenyl is also used as a fungistatic agent in the preservation of citrus fruits. Leaks from heat transfer systems may obviously be associated with thermal burns. Vapors of these compounds are irritating to the eyes and upper airway. Experience of Finnish observers (Hakkinen et al., 1973) suggests that diphenyl exposure may be associated with nonspecific gastrointestinal symptoms, polyneuritis with pain and numbness, and headache. Objective changes in electroencephalograms and electroneuromyograms were reported among workers impregnating fruit wrappers with diphenyl. In addition there were biochemical abnormalities in hepatic function, abnormal hepatic cellular changes in liver biopsy tissue, and evidence that death of one exposed worker was due to acute yellow atrophy of the liver.

NAPHTHALENE

Naphthalene, familiar as "moth balls" (not paradichlorobenzene), is used primarily as a chemical intermediate in the production of phthalic acid and derivatives for the dye and plastics industry. The vapors cause eye irritation, headache, and a warm feeling of the skin with profuse sweating. Lenticular opacities have been observed in a number of workers exposed to high concentrations (Ghetti and Mariani, 1956). High levels of exposure, such as may be associated with ingestion, can cause an acute hemolytic anemia especially in individuals with erythrocytic deficiency of glucose-6-phosphate dehydrogenase.

CHLORINATED HYDROCARBONS • 3

NATURE OF CHLORINATED HYDROCARBONS

Simple chlorinated hydrocarbons have a widespread and essential role in the chemical industry and in a variety of manufacturing operations. In the chemical industry these compounds provide the principal routes by which chlorine reaches the chemical market for use in plastics, pesticides, and other chlorinated organic compounds of great economic significance. As solvents the simple chlorohydrocarbons are widely used because of their excellent solvent properties for oils, waxes, fats, and various organic molecules, their relative cheapness, and the nonflammable characteristics associated with most of them. Accordingly they are valuable extractants, dry cleaning agents, surface degreasing compounds, and vehicles for paints, varnishes, and other industrial coatings. Some chlorohydrocarbons are constituents of paint removers. For many years carbon tetrachloride was used in the so-called Pyrene fire extinguisher, an application which has been almost universally discontinued because of the toxic properties of the extinguishant and its degradation products.

Although the number of readily available solvent chlorohydrocarbon compounds is very large, about a dozen of them are of industrial significance and, as such, are of potential occupational medical importance. It is useful to be familiar with the nomenclature of these compounds to avoid a possible confusion when the several common or technical names are used. Not all compounds listed in Table 7 are widely used.

Table 7
Chlorohydrocarbon Solvents

Common Name	Chemical Name	Formula
Methylene Chloride	Dichloromethane	CH_2Cl_2
Chloroform	Trichloromethane	$CHCl_3$
Carbon Tetrachloride	Tetrachloromethane	CCl_4
Ethylene dichloride	1,2-Dichloroethane	$CH_2Cl\,CH_2Cl$
Ethylidene dichloride	1,1-Dichloroethane	$CH\,Cl_2\,CH_3$
Vinyl trichloride	1,1,2-Trichloroethane	$CH_2Cl\,CH\,Cl_2$
Methyl chloroform	1,1,1-Trichloroethane	$CH_3\,C\,Cl_3$
Acetylene tetrachloride	1,1,2,2-Tetrachloroethane	$CH\,Cl_2\,CHCl_2$
Acetylene dichloride	1,2-Dichloroethylene (Cis & Trans)	$CHCl = CHCl$
Acetylene trichloride / Trichloroethylene	Trichloroethylene	$CHCl = CCl_2$
Perchloroethylene	Tetrachloroethylene	$CCl_2 = CCl_2$

Many of the members of this series of compounds are extremely volatile, a property which permits a hazardous exposure to occur more rapidly than might be anticipated by the inexperienced worker. While many such compounds are of relatively low chemical toxicity, the rate at which a hazardous atmospheric concentration of the solvent may be achieved may be very rapid. Consequently a relatively high Threshold Limit Value rating may be misinterpreted as a low hazard rating. In view of the rate at which an atmospheric hazard may develop, special caution is necessary in certain industrial situations, especially those in which the application of heat may further increase the air levels of solvent materials. As with many categories of industrial solvents, mixtures of compounds are the rule although the material is sold in commerce under a single chemical or common name. While this may be of no particular health significance because of a similarity between the effects associated with many specific compounds, there are several molecules of clearly greater toxicity. Inquiry as to purity is therefore an essential element in the investigation of working conditions or possible etiological factors in disease.

Chlorohydrocarbons may be thermally decomposed (cracked) at high temperatures to yield, among other things, hydrogen chloride and phosgene gases. The former is a highly irritant toxic gas, which, because of its irritant effects upon the mucous membranes of the eyes and upper airway, has excellent warning properties which tend to limit exposure. Phosgene, on the other hand, is the classical insidious deep lung irritant without significant sensory effects to warn of its presence. When chlorohydrocarbon vapors are thermally cracked in open flames or arcs associated with furnaces, boilers, or welding apparatus, sufficient phosgene may be generated to create a hazard of far greater magnitude than that associated with the airborne solvent vapors alone. The amount of phosgene production varies with the compound being cracked and the conditions of heating, moisture and hot ferrous surfaces apparently contributing to phosgene production. While phosgene poisoning from this type of exposure has not been common, it is obviously important to isolate heating and welding operations from atmospheres containing chlorohydrocarbon vapors. Temperatures of the burning cigarette are high enough to decompose these vapors, but there is no evidence that smoking has ever produced phosgene or phosgene poisoning. In situations where exhaust gases from furnaces may contain cracked solvent products containing hydrogen chloride, special attention should be paid to the duct work inasmuch as it is unusually susceptible to corrosion

with attendant leaks and the release of carbon monoxide into the work space.

Compounds of the chlorohydrocarbon group are most commonly absorbed through the lungs, although absorption from the gastrointestinal tract does occur in cases of ingestion. Absorption through the skin occurs, but it is of no known practical industrial significance except possibly in the case of carbon tetrachloride, which may penetrate the skin in toxic quantities.

For the most part, chlorinated hydrocarbons which enter the body through pulmonary gas exchange surfaces leave the body unchanged via the same route. Those compounds which are metabolized may appear as degradation products in the urine. Techniques developed by Stewart have permitted the retrieval of solvent vapors from the exhaled air of exposed workers and the analyses of these vapors to characterize various quantitative and qualitative aspects of the exposures. Using the long path-length gas cell of an infrared spectrometer or the gas chromatograph, he has been able to demonstrate the continuing exhalation of tetrachloroethylene vapors more than 350 hours after the conclusion of exposures (Stewart et al., 1961b). Chlorohydrocarbons which are actively metabolized, of course, disappear from the breath much more rapidly, e.g., trichloroethylene (Stewart et al., 1961a). In cases of suspected exposure to these materials, the breath collection and analysis technique permits the identification of solvents and the construction of breath excretion curves which can be used to estimate the quantity of material absorbed.

OCCUPATIONAL DISEASE CAUSED BY TOXIC CHLOROHYDROCARBONS

As a group, the chlorohydrocarbons share several biological properties. Other biological properties are associated with only certain members of the series, and these manifestations may vary over a wide spectrum according to which compound is responsible for the poisoning. This intercompound variability has been most clearly examined experimentally in situations in which the liver is the target organ. In the ingenious work of Plaa and his colleagues (1958) hepatotoxicity in mice was evaluated by judging the impairment of detoxication of barbiturates after exposure to members of the chlorinated hydrocarbon series. More recently hepatic damage has been evaluated in mice by determination of the serum glutamicpyruvic transaminase (SGPT) levels after exposure (Gehring, 1968). These experimental studies are in general agreement with each other and with clinical evidence which has accumulated over the years from cases of human overexposure. In order of decreasing hepatotoxicity are carbon tetrachloride, chloroform,

1,1,2-trichloroethane, tetrachloroethylene, trichloroethylene, methylene chloride, and 1,1,1-trichloroethane.

A characteristic property of all the members of this series is the ability to depress the central nervous system, leading through the several stages of clinical anesthesia ultimately to death from respiratory paralysis. This property is well known, for indeed chloroform and trichloroethylene have been used as surgical anesthetics. While there is undoubtedly a difference between the anesthetic potencies of the chlorohydrocarbons, the generally observed phenomena in man are typical of the group. These include dizziness,confusion, drowsiness, nausea, vomiting, and occastonally abdominal pain. There may be visual disturbances. Deep anesthesia may lead to death from respiratory depression or circulatory failure. Actual anesthesia is not commonly encountered in industry unless the worker enters tanks or confined places, or there is spillage, gross misuse of materials, or intentional inhalation of vapors to produce euphoria or a "jag." It is not uncommon, however, to receive reports of vague nonspecific psychological or psycho-physiological reactions associated with exposures to chlorohydrocarbons. Headache, fatigue, irritability, impaired memory, anorexia, and nausea are typical symptoms. Whether or not there is an actual pharmacodynamic explanation for these complaints has not been established.

There have been several reports over the years of sudden death in apparently healthy individuals who had been exposed to chlorohydrocarbons of relatively low toxicity. Autopsies in such cases have failed to reveal a cause of death. The possibility that death was related to transient ventricular fibrillation cannot be excluded. There is experimental evidence that chlorohydrocarbons sensitize the myocardium to the effects of endogenous epinephrine (Reinhardt et al., 1971; Aviado and Belej, 1973).

The vapors of the chlorohydrocarbons are not especially irritating to the mucous membranes of the eyes and upper airways. Prolonged contact of these solvents with the skin can result in extreme dryness and fissuring with associated infection. This phenomenon is secondary to the "degreasing" effects of these materials on the skin. The incidence of sensitization is very low. Immersion of the fingers in methylene chloride leads to severe pain with transient numbness; pain with trichloroethylene and carbon tetrachloride is less severe; with methylchloroform and perchloroethylene it is minimal.

METHYL CHLORIDE

Methyl chloride, a colorless gas at room temperatures, is handled in industry under pressure in the liquid state. It is used almost

exclusively in the chemical industry as a methylating agent in the production of silicones, butyl rubber, and tetramethyl lead. Its use as a domestic refrigerant, the most common source of intoxication in the past, has almost entirely ceased.

Methyl chloride is a potent narcotic causing headache, drowsiness, giddiness, ataxia and, ultimately, convulsions, coma and respiratory failure. Several cases of long-standing neuropsychiatric alterations have been described: depression, change of personality, irritability, insomnia, disturbances of vision. It is difficult—if not impossible—to unequivocally associate these manifestations with a specific toxic effect of the suspected compound.

METHYLENE CHLORIDE

Methylene chloride is used as a solvent and extracting agent where a high degree of volatility is desired. It is a common constituent of paint strippers. It is the least toxic of the four chlorinated methane derivatives. Because of its high volatility, it is easy to achieve air levels which result in "drunkenness" and associated unreliable behavior. The current threshold limit value (TLV) of 500 ppm is probably excessive in view of the fact that exposure to methylene chloride in the range of 500 to 1,000 ppm can result in CNS depression in some persons (Stewart et al., 1972). It is of additional importance that exposures to this compound are followed by increases in the carboxyhemoglobin level, presumably as a result of metabolism of solvent to carbon monoxide. Experimental exposure of human subjects to methylene chloride at 1,000 ppm for two hours has resulted in carboxyhemoglobin saturation levels in excess of those permitted in the workplace from exposure to carbon monoxide alone (Stewart et al., 1972). That the CNS effects of carbon monoxide and methylene chloride are at least additive is evidence for reduction in the permissible levels of industrial exposure.

CHLOROFORM

Chloroform, or trichloromethane, is unimportant as an industrial solvent or intermediate. Its effects are not unlike those associated with carbon tetrachloride. One of the authors (HLH) has cared for two hospital laboratory technicians exposed to chloroform who complained of nausea and anorexia. Their liver function tests were abnormal.

CARBON TETRACHLORIDE

Carbon tetrachloride has lost its early predominance as a cheap nonflammable chlorinated solvent for use in degreasing, dry cleaning, and extracting. Less toxic compounds such as tri- and tetrachloroethylene have served as admirable substitutes. Carbon tetrachloride "Pyrene" fire extinguishers are also now obsolete.

The annual production of carbon tetrachloride continues to increase, however, with most of the output (80 percent) going into the synthesis of chlorofluoromethane refrigerants, solvents, and aerosol propellants. Relatively smaller amounts of carbon tetrachloride continue to be used as solvents (as in chromatography), in the recovery of tin from scrap metal, as an insecticidal grain fumigant, and as an addition to solvent mixes to lower their flammability.

toxicity

Accumulating evidence over the years has shown carbon tetrachloride to be one of the most toxic of the common solvents. It is a potent narcotic and, as such, has properties not dissimilar to other compounds in the series. In addition, however, this compound has specific toxic effects upon the liver and kidneys. When exposure has been of sufficient magnitude to cause visceral injury, the liver and kidney are commonly both affected although not necessarily to the same degree. Renal injury has been considered the prime manifestation of poisoning following inhalation, and hepatic damage has been thought to be predominant when carbon tetrachloride has been ingested. The evidence does not give support to this point of view. Nausea, vomiting, and abdominal cramps have been considered the primary presenting symptoms suggesting liver injury. Such symptoms have appeared in the absence of altered liver function tests, however, suggesting that in some situations this pattern of complaints may represent a nonspecific effect. Nausea and vomiting usually appear within hours after exposure although a delay up to six days has been noted, probably depending on the quantity and rate of absorption. The abdominal pain has been misinterpreted as indicative of acute appendicitis.

Tests of hepatic function, especially those based upon a determination of hepatic enzyme levels in the serum, may give evidence of liver injury well in advance of clinical signs. Serum glutamic oxaloacetic transaminase (SGOT) levels in excess of 25,000 units have been reported following acute nonfatal carbon tetrachloride poisonings. Maximal liver damage most probably occurs within forty-eight hours of an acute exposure. In severe injury the liver is invariably enlarged and tender, jaundice may be present, and hepatic failure with ammonia intoxication may ensue.

The mechanism of carbon tetrachloride hepatotoxicity has been examined in great detail by Recknagel (1967). The collected evidence indicates that the two prime pathologic observations, fatty degeneration and necrosis, have distinct pathogeneses. The hepatic accumulation of lipid is related to injury of the endoplasmic

reticulum and disruption of the mechanism for moving lipid out of the liver through the coupling of triglycerides to the lipoprotein carrier. Although the precise mechanism for the necrosis is not clearly established, it is apparently associated with the intracellular release of destructive hydrolytic lysosomal enzymes, injury to mitochondria with loss of energy sources, and general metabolic chaos subsequent to loss of cytoplasmic enzymes and coenzymes.

While the intact carbon tetrachloride molecule may cause damage to the hepatic cell wall, prime damage is caused by metabolites of the solvent, perhaps CCl_3 radicals. Cells which do not actively metabolize carbon tetrachloride have been shown to be relatively resistant to this compound. Conversely, measures which enhance metabolic ability by stimulating endoreticular expansion and enzyme induction also enhance carbon tetrachloride toxicity (Garner and McLean, 1969). Following this line of reasoning, one may consider that the increased vulnerability of alcoholics to the hepatotoxicity of carbon tetrachloride may be due to the fact that alcohol leads to the induction of metabolising enzymes of the endoreticular system.

Renal impairment is common and may exist in the absence of demonstrable hepatotoxicity (Guild et al., 1958). Costovertebral pain is not uncommon, proteinuria is characteristic, and anuria may occur some one to seven days after an acute exposure and persist for one to fifteen days. An examination of urinary sediment reveals evidence of acute tubular necrosis: red and white blood cells, hyaline, granular, and red cell casts, and renal tubular epithelial cells. The development of the uremic syndrome or potassium intoxication are indications for hemodialysis. The evidence is that the observed nephrotoxicity is due to the direct effects of carbon tetrachloride upon the proximal tubule and loop of Henle, although the distal tubule is affected to a lesser degree. The prognosis in severe cases of carbon tetrachloride poisoning has improved markedly since the availability of dialysis has become common. The simultaneous presence of hepatic failure with impaired urea synthesis and ammonia intoxication is obviously unfavorable. Recovery may require months but may be eventually complete.

There is no universal agreement as to whether or not acute hepatorenal injury or prolonged exposure without acute phenomena may result in chronic impairment of organ systems. There have been enough cases of cirrhosis following long exposure, however, to suggest very strongly that the association can be causal in specific instances (McDermott and Hardy, 1963). Hepatocellular carcinoma developing seven years after acute car-

bon tetrachloride intoxication has also been reported (Tracey and Sherlock, 1968), and this compound is a potent hepatocarcinogen in animals. It is of course possible that regeneration itself in these cases is the precancerous lesion and that carbon tetrachloride is not a specific carcinogenic material.

A bleeding tendency has been observed in many cases of actue carbon tetrachloride poisoning. In some cases it may reflect visceral damage. In others bleeding may be a consequence of aplastic anemia. The evidence that carbon tetrachloride is a direct bone marrow poison is not indisputable, but cases have been presented in which the nature of the exposure and the sequence of events are reasonably convincing (Straus, 1954).

ETHYL CHLORIDE

Ethyl chloride is a gas at room temperature; however, it is easily liquefied and is familiar to physicians as a local anesthetic agent which freezes the skin when the agent is applied as a spray from a glass cylinder. Ethyl chloride is found in industry almost entirely as a chemical intermediate used in the synthesis of tetraethyl lead and other ethyl compounds. The physiological properties of ethyl chloride are related to its anesthetic effect and perhaps to its cardiotoxic properties as a sensitizer of the myocardium to endogenous epinephrine. As far as is known, this compound is excreted via the lungs without significant metabolic degradation in the body.

ETHYLENE DICHLORIDE

The ethylene dichloride, or ethylene chloride, of industry is 1,2-dichloroethane. 1,1-Dichloroethane is commonly known as ethylidene dichloride or ethylidene chloride. These are saturated compounds, chlorinated ethanes, and the "ene" endings should not lead to confusion of those compounds with dichloroethylene. Much of this terminology is quite unfortunate, but is so well established among the various industrial traditions that change is unlikely.

Both chlorinated ethanes are used as solvents and as chemical intermediates. They are irritating to the eyes and the respiratory tract, producing salivation, sneezing, and coughing. In those few cases of intoxication which have been reported, the anticipated anesthetic effects have been observed with associated dizziness, nausea and vomiting. In severe and fatal cases hepatic and renal injury have been observed.

METHYL CHLOROFORM

Methyl chloroform (1,1,1-trichloroethane) is a chlorohydrocarbon solvent which, because of its very low toxicity (Stewart, 1971), is being utilized at an accelerated rate. It is widely applied as a

vapor degreaser, dry cleaning agent, aerosol vehicle, and cold cleaner. Like many chlorohydrocarbons, methyl chloroform is somewhat unstable, and small amounts of stabilizing compounds are added to the solvent material sold in commerce. Such stabilizers or inhibitors may be various ketones, alcohols, esters, nitrogen compounds, etc., which do not change the toxicity of the commercial product sold under trade names such as Chlorothene or Triethane.

harmful effects

Methyl chloroform is a narcotic and skin defatting solvent as are the chlorohydrocarbons in general. Exposures to high air concentrations of methyl chloroform may lead to narcosis and even fatal respiratory depression under conditions of grossly negligent overexposure. There is no evidence that this solvent causes hepatic or renal injury such as is characteristic of carbon tetrachloride. Experimental work (Reinhardt et al., 1971; Aviado and Belej, 1973) and clinical experience with anti-tussive preparations containing trichloroethane identifies serious cardiotoxic properties of this compound, and deaths have been attributed to cardiac arrhythmias, probably mediated through epinephrine sensitization.

1,1,2-Trichloroethane, vinyl trichloride, an isomer of methyl chloroform, is a more potent anesthetic agent, an irritant to mucous membranes, and a significant hepato- and nephrotoxin. It does not have major industrial uses.

TETRACHLOROETHANE

Industrial references to acetylene tetrachloride or tetrachloroethane are invariably to the symmetrical isomer of 1,1,2,2-tetrachloroethane. Clinical evidence indicates that this compound is by far the most poisonous of the chlorohydrocarbons used as industrial solvents. Unfortunately from the health point of view, it is an excellent solvent, often the best available for many applications. Early utilization of tetrachloroethane as a vehicle for the so-called dope to cover airplane fabrics led to numerous severe and fatal cases of toxic hepatitis and atrophy of the liver. The compound is the best solvent for cellulose acetate, which for many years was the best available coating material for fabrics to be used in aviation and products requiring a thin, light, impervious surface.

The recognized toxicity of tetrachloroethane has caused it to be eliminated from most industrial uses unless its specific solvent properties are necessary. The use of this compound is rarely justified. Toxic manifestations resemble those associated with carbon tetrachloride; however, the hepatotoxicity of tetrachloroethane is much more prominent.

DICHLOROETHYLENE

1,2-Dichloroethylene or acetylene dichloride is handled in commerce as a mixture of the trans and cis isomers. The material is used as a low-temperature extracting agent for heat-sensitive substances such as perfume oils and caffeine in coffee. Aside from the narcotic properties of this solvent, toxic effects have not been prominent in the rather small-scale industrial usage which exists.

VINYLIDENE CHLORIDE

The 1,1-isomer, or vinylidene chloride, is used almost entirely as a monomer in the manufacture of copolymeric plastics. Experience from the synthetic plastics industry indicates that 1,1-dichloroethylene has toxicological properties which are similar to those of carbon tetrachloride, i.e., there is significant hepato- and nephrotoxicity.

TRICHLORO-ETHYLENE

Trichloroethylene is utilized in very large quantities as a metal degreaser and dry cleaning agent, applications requiring over 90 percent of the amount produced. Minor amounts of the solvent are used in the extraction of fats from fish meal and other natural products, in the manufacture of adhesives and industrial paints, and in the dewaxing of lubricating oils. Trichloroethylene is often used as a substitute for carbon tetrachloride, which has significantly greater toxic properties. Because of its relatively low toxicity and nonflammability, trichloroethylene has been used in clinical medicine as a surgical anesthetic agent under the names Trilene, Trimar, or Trethylene. This use has been largely abandoned because of the availability of better anesthetic agents and because of several anesthesia accidents related to the generation of dichloroacetylene when trichloroethylene was passed through a closed-circuit apparatus in which a soda-lime carbon dixoide absorber was used. In some situations trichloroethylene has been used as an obstetrical analgesic inhalant, often self-administered by the woman in labor.

Trichloroethylene is readily absorbed and excreted via the lungs. In addition it is metabolized in the liver, and a principal metabolite, trichloracetic acid (TCA), appears in the urine. Trichloracetic acid may be detectable in the urine for several weeks after exposure has terminated. Urinary assays for trichloracetic acid and trichloroethanol are widely used in Europe in the medical surveillance of workers exposed to trichloroethylene. It is the more common practice in the United States to estimate the atmospheric concentrations of this material in the worker's breathing zone using a properly calibrated halide meter or detector tubes. In situations where the ambient air levels or exposures vary widely, it is possible to monitor the trichloroethylene concentrations in the ex-

haled breath of persons exposed (Stewart et al., 1970). The material is excreted exponentially via the lungs, most of the absorbed amount being exhaled during the first twenty-four hours following exposure. Samples of exhaled breath are easily collected in Saran bags and analyzed by infrared spectroscopy or gas chromatography. By making serial evaluations during the post-exposure period, the physician may obtain sufficient information to establish the excretion rate and an estimate of the previous vapor exposure. Stewart has presented evidence that data thus obtained are more accurate, more useful, and more easily obtained than those derived from determinations of urinary metabolites.

toxicity

The narcosis produced by absorption of trichloroethylene cannot be distinguished from that related to the absorption of other chlorohydrocarbons. There may be an excitatory or euphoric stage. In some cases this euphorizing tendency has led to "addiction" and the repeated intentional inhalation of the vapor (Harenko, 1967). There may be dizziness, confusion, drowsiness, and eventually loss of consciousness. While most manifestations clear promptly with the breathing of uncontaminated air and the excretion of the solvent via the lungs, there is evidence of neurological disturbances of longer duration. These may affect the peripheral nerves predominantly, although the central nervous system may show similar involvement. Feldman and Mayer (1968) have demonstrated a slowing in conduction time which is reversible over the course of months. Various psychosomatic complaints and uncommon toxic psychoses have also been described (Hamilton and Hardy, 1949, p. 381).

There is some dispute in the clinical literature as to the extent to which trichloroethylene can produce toxic effects unrelated to nonspecific chlorohydrocarbon narcosis. Enzyme and urinary urobilinogen studies after exposures at 200 ppm have yielded no evidence of hepatotoxicity. On the other hand, the report by Priest and Horn (1965) of acute fatal toxic hepatitis in a man operating a trichloroethylene degreaser is typical of those which report hepatic injury. In many of these cases the environmental investigations leave much to be desired, and the question of contaminants, inhibitors, or other exposures is always raised. While many of these reports may be in fact misleading, a careful reading of the histories suggests the likelihood of hepatotoxicity in some individuals. The concurrent ingestion of alcoholic beverages has been described as contributory. In the usual industrial exposure, however, it would be inaccurate to suggest that trichloroethylene is a potent hepatotoxin. Evidence that trichloroethylene is a nephrotoxin was

presented by Gutch et al. (1965), who described acute renal failure and toxic myocarditis in a man who had used this solvent in cleaning floors with the rag and bucket technique. Other reports of similar cases are not known. Convincing evidence of hematopoietic damage is absent.

Sudden death in young workers exposed to trichloroethylene has been described by a number of observers (Kleinfield and Tabershaw, 1954). In spite of the lack of supporting anatomical information, the inference that these deaths were due to ventricular fibrillation is reasonable.

Trichloroethylene vapors are mildly irritating to the eyes and upper airway of some individuals. In many cases these subjective complaints are not reported on repeated or continuing exposure. Open flames and heated surfaces may cause the pyrolysis of this compound to the highly toxic gas, phosgene.

PERCHLORO-ETHYLENE

Tetrachloroethylene or perchloroethylene is the principal dry cleaning solvent for clothing and is commonly used as well in degreasing operations. Its toxicological properties parallel very closely those associated with trichloroethylene.

harmful effects

The narcotic properties of tetrachloroethylene have been most frequently demonstrated in dry cleaning shops with ineffective ventilation or solvent recovery equipment. There have been an unfortunate number of cases of fatal central nervous system and respiratory depression related to the use of sleeping bags or other heavy articles which had not been thoroughly cleared of the solvent prior to use. The typical story describes the cleaning of a sleeping bag in a coin-operated dry cleaning establishment, failure to air the bag in the open for a period sufficient to permit the evaporation of retained solvent, and failure of the owner to awaken following a night's rest in the bag.

Vapors are rapidly absorbed through the alveolar epithelium and are excreted via the same route. Absorption may cause lightheadedness, confusion, and the entire spectrum of narcotic phenomena. The vapors may have a direct, mildly irritating effect upon the eyes and upper airway. The evidence for viscerotoxic effects is similar to that for trichloroethylene. Stewart (1969) noted abnormal liver function tests after exposure, finding SGOT and SGPT levels to reach maxima in about three days. Asymptomatic individuals, who had totally recovered, showed elevated urinary urobilinogen and total serum bilirubin levels seven to ten days after exposure. Stewart raises the question of whether or not acute renal failure, rarely observed in these cases, may be due to shock

after peripheral vascular collapse in deep central nervous system depression.

Exposure is evaluated either by environmental measurement or by determining the level of the solvent in exhaled breath (Stewart et al., 1961b). Alveolar breath analysis permits the identification of tetrachloroethylene two weeks after exposure, and serial determinations provide an estimate of the magnitude of exposure.

CHLORINATED BIPHENYLS AND CHLORINATED NAPHTHALENES

Chlorinated biphenyls (polychlorinated biphenyls, PCB's) and chlorinated naphthalenes are prepared from diphenyl and naphthalene which may be reacted to varying degrees with chlorine to produce a number of compounds designated by various trade names such as Aroclor and Halowax. The materials found in commerce are invariably mixtures of specific molecules, and the commercial product is often described in terms of the relative proportion of chlorine. High degrees of chlorine substitution are associated in general with higher toxicities. As the toxicological properties of the chlorinated biphenyls and naphthalenes are not noticeably dissimilar, such mixtures are considered to have biological properties which are common to the components.

These materials vary in form from oily liquids to waxy or hard solids. Because of their chemical stability and high dielectric constants, they are widely used in cable insulation and as impregnants for electrical capacitors. Chlorinated biphenyls and naphthalenes are also used for surface coatings—for example, in paints, plastics, and varnishes, and in extreme pressure lubricants which are subject to highly oxidizing conditions, high temperatures, or submersion. Heat-transfer media may also contain materials of this type as may certain cutting fluid additives and components of carbonless copy paper systems.

toxic effects

Chlorinated biphenyls and naphthalenes are potent inducers of chloracne, which may develop after weeks or months of cutaneous exposure and commonly appears first lateral to the eyebrows, on the chin, cheeks, forehead, chest, abdomen, thighs, or buttocks. A history of acne vulgaris is not necessarily present, but direct local contact with the compound over a period of time will be evident. The lesions are primarily papules and yellowish cysts surrounded by mild erythema. Comedones, a common feature of acne vulgaris and oil folliculitis, are usually absent, as is melanosis. Pruritis is common. Chloracne, also known in various trades as "cable rash," is the clinical manifestation of a specific effect of these materials upon the pilosebaceous unit. The chlorinated biphenyls and naphthalenes alter the differentiation of the sebaceous gland

cells so that keratinocytes form to plug the unit and create keratin-containing cysts.

therapy and control

The therapy of chloracne is based upon termination of exposure to the offending materials and application of those measures which are commonly used to control acne. Prevention through the use of protective clothing, showers, and appropriate clean clothes and lockers is necessary. Barrier creams have been of little, if any, utility in the control of chloracne.

When compounds of this group are used in poorly ventilated areas and especially when heat is applied, as in welding or cable splicing, there may be significant systemic absorption of toxic vapors. The target organ is primarily the liver, and cases of fatal acute yellow atrophy have been reported. The physiological mechanism related to this clinical course is not understood. Workers who are exposed to this class of materials, especially to the more highly chlorinated compounds and particularly when volatilizing temperatures are encountered, should receive the benefit of periodic liver function tests.

Environmental dissemination of the chlorinated biphenyls and the identification of these materials in plant and animal tissues has become a matter of great international concern. While the full significance of this contamination is yet to be established, clinical experience with toxic exposures of nonoccupational origin emphasizes the biological properties of this class of compounds. An epidemic of "Yusho" ("oil disease") in Japan, related to the contamination of rice oil with polychlorinated biphenyls, was marked by swelling of the eyelids, chloracne, hyperpigmentation of the skin, and nonspecific digestive or neurological symptoms (Katsuki et al., 1972). Recovery from "Yusho" has been slow, and the disorder, which has affected over 1,000 persons, has been a major medical and social problem in several prefectures of western Japan.

Compounds of this category have been associated with systemic disease in cattle and poultry. The extent to which the disease phenomena in man and animals are due to substances other than polychlorinated biphenyls and naphthalenes but present as industrial contaminants remains to be established (Kimbrough, 1972). Such contaminants which have come under intense suspicion include tetrachlorodibenzofurans and tetrachlorodibenzodioxins.

PARADICHLORO-BENZENE

White or colorless crystals or "nuggets" of paradichlorobenzene are commonly available as "moth-proofing" materials used by homeowners to protect woolen garments. Naphthalene, a less effective but strongly aromatic compound, has also been used for

this purpose but has been largely superseded. At high concentrations, the vapors of paradichlorobenzene are strongly irritating to the eyes and upper airway. This serves to limit exposure to high concentrations of this volatile compound. There is evidence of hepatic and renal injury in experimental animals, but similar phenomena in humans have not been documented. Cataracts, attributed in rare instances to "moth-proofing" materials, are probably better related to naphthalene than to paradichlorobenzene. Animal evidence supports this view.

OTHER HALOGENATED HYDROCARBONS • 4

The vast majority of industrial halogenated hydrocarbons are those which contain chlorine—usually without, but occasionally with, other halogen constitutents. Fluorinated compounds are found in a relatively small number of specific materials, although the growth of the fluoro-organic chemical industry is impressive. Industrial bromine-containing organics are even less common, and the iodine derivatives are rare.

Those fluorine-containing hydrocarbons which have commercial application include the simple compounds, often containing chlorine as well, which are marketed with familiar names such as Freons or Geons among others. These compounds are used as propellants in aerosol "bombs" or can-dispensers, as refrigerants, and as solvents for special or critical applications where their relatively high cost is warranted. As a group these compounds have been thought to lack biological properties or to have mild, reversible depressant effects on the central nervous system. More recent evidence (Reinhardt, et al., 1971; Aviado and Belej, 1973) draws attention to the prominent cardiotoxic effects, manifested in arrhythmias, that are associated with pulmonary exposure to fluorocarbons, especially fluorocarbon 11 (trichlorofluoromethane), fluorocarbon 21 (dichloromonofluoromethane) and fluorocarbon 113 (trichlorotrifluoroethane). Sensitization of the heart to epinephrine is implicated in most of the arrhythmias, but the mechanism is not well understood. In experimental animals variable degrees of tachycardia, myocardial depression, and hypotension have been described.

Polymerized fluoroethylene and similar fluoro-chloro compounds are used in plastics of the so-called Teflon and Kel-F type and are described under that classification. Organo-fluorine compounds which may decompose or be metabolized to monofluoroacetic acid have a specific effect upon the tricarboxylic acid cycle and may be extremely toxic.

METHYL BROMIDE

Methyl bromide is a heavy colorless gas used in fumigating warehouses, grain stores, the soil, and other enclosed areas or areas which can be sealed off with impervious plastic sheeting. The gas has a density over three times that of air; consequently, methyl bromide tends to collect in low places. It penetrates easily into bales or sacks of material and is, therefore, a highly effective non-

residual insecticidal material. The gas is highly toxic to man and has most commonly caused injury among fumigating operators and others who enter structures when gas is still present prior to post-treatment ventilation. The compound has also been associated with occupational injury in the course of its use as a methylating agent in synthetic chemical operations and as a fire extinguishing agent in special or now obsolete appliances. Methyl bromide was also formerly used as a refrigerant gas, but it has been superseded for this purpose by ammonia or the fluorohydrocarbons.

The gas has no warning properties, and those who use it are well advised to have suitable monitoring instruments and personal protective equipment. Methyl bromide is readily absorbed through the lungs. Transcutaneous absorption may occur, but it is not considered to be of significance in occupational poisoning.

reports of harmful effects

Acute exposure to excessive concentrations of methyl bromide produces headache, nausea, and vomiting. Some patients have described a disagreeable taste to food—bitter or "like burned rubber." The gas is a delayed pulmonary irritant and can produce bronchitis, pneumonia, and pulmonary edema. Neurological effects are more common, often severe, and frequently characterized by a prolonged clinical course. Such effects may be delayed in onset by a latent period which follows the termination of exposure by hours or even days, the delay possibly determined by the amount inhaled during the worker's activity. In cases of mild exposure, neurological phenomena may consist of giddiness, ataxia, vertigo, paresthesias, and weakness. Twitching and epileptic seizures may occur. More severe episodes are associated with status epilepticus, prolonged loss of consciousness, and pyramidal or extra-pyramidal signs (Rathus and Landy, 1961). These manifestations may be very slow to resolve, and ataxia and seizure patterns may persist for months or years. In some cases; with or without a prolonged latent period, a fatal outcome or permanent neurological or psychiatric sequelae may result.

Neurological reactions occur at levels of exposure which are insufficient to produce acute or delayed pulmonary manifestations. The altered physiological functions in methyl bromide poisoning are not understood, although there has been speculation that the clinical manifestations represent an unusual form of bromidism in which the distribution of inorganic bromide is related to hydrolysis of the organic compound after it has been distributed. Methyl bromide is also a potent methylating agent and may act by this mechanism.

There are no specific treatments for either the pulmonary or neurological forms of methyl bromide poisoning.

Splashes of liquid methyl bromide on the skin may produce a pruritic inflammatory reaction. Repeated splashes or prolonged exposure may lead to a severe burn with vesicles. Vapors may become adsorbed by clothing and shoes to represent a relatively potent source of skin contact. Direct contamination of shoes may cause severe burns.

ETHYLENE DIBROMIDE

Ethylene dibromide is a scavenger for lead in anti-knock fluids for gasolines. The compound is also used as a fumigant, fire extinguishant, special solvent, and gauge fluid. Clinical experience with this material is very limited, although the evidence suggests that it is locally irritating and is a central nervous system depressant. It has a low vapor pressure, a property which tends to limit air levels.

ACETYLENE TETRABROMIDE

Acetylene tetrabromide is a very dense organic compound used as an ore flotation agent and as a gauge fluid. It is a central nervous system depressant but has a very low vapor pressure at ambient atmospheres. Consequently clinical problems are not generally anticipated.

ALCOHOLS AND GLYCOLS • 5

In the industrial setting alcohols and glycols do not present serious hazards. Although specific compounds (e.g., methanol and ethylene glycol) continue to be identified as causal agents in epidemics or isolated instances of intoxication, the observed illness is almost invariably associated with the intentional oral ingestion of these compounds. Industrial exposures to vapors of alcohols and glycols rarely—if ever—produce symptoms of systemic intoxication, and whatever toxicity is observed is usually related to irritation of the conjunctivae and mucous membranes of the upper airway. In most industrial situations only the low-molecular-weight alcohols are sufficiently volatile to yield significant air concentrations. The alcohols and glycols have narcotic properties; however, these are much less prominent than those associated with solvent hydrocarbons or halogenated hydrocarbons.

METHANOL

Methanol (methyl alcohol, wood alcohol, wood spirit, carbinol) is used extensively as a solvent for lacquers, plastics, and various industrial coatings. It is easily available outside industry as a component of lacquer thinners, anti-freeze of the "nonpermanent" type, and canned heating preparations of jellied alcohol. Most gasoline additives to prevent winter fuel line and carburetor icing are based on methanol. The designation "wood alcohol" implies that methanol is derived from the distillation of wood; however, the production of synthetic methanol today from carbon monoxide and hydrogen is of much greater importance.

toxic effect

The early literature does describe examples of systemic intoxication by the inhalation of methanol in various varnishing operations or similar situations in which large quantities of solvents were being evaporated into an enclosed space. While the possibility of ingestion cannot be definitely excluded in every report, it is probable that some of these exposures were, in fact, only by the respiratory route. The levels of such exposures, however, must have been extremely high, for there is ample evidence today from the photographic film industry that repeated exposures to air levels of methanol well in excess of the threshold limit value of 200 ppm do not cause illness or significant discomfort.

The onset of symptoms may follow ingestion by a period of less than an hour or may be delayed for thirty hours; a latency period of twelve to eighteen hours is common. In the usual case of poisoning by ingestion the initial symptoms may include those

suggestive of ethanol intoxication: headache, weakness, vertigo, visual disturbances, and coma (Roe, 1946; Roe, 1955; Bennett et al., 1953). There may be nausea, vomiting, and abdominal or lumbar pain. The symptoms are associated with metabolic acidosis, reflecting the accumulation of acid metabolites and their effects upon normal metabolic systems. It is believed that the severity of symptoms is proportional to the intensity of the acidosis.

Visual disturbances, the most striking and often the most damaging aspect of methanol intoxication, may develop early (Benton and Calhoun, 1952). A blurring of vision, occasionally with changes in color perception or with scotomata, may develop promptly with little warning. The loss of acuity may be accompanied by the perception of spots or a gray mist sensation, and there may be pain or tenderness of the eyes or photophobia. The initial impairment of vision may be transitory, although the improvement in vision may be followed by complete and permanent blindness. Clinical observations suggest that if there is no improvement within six days the prognosis is very poor. Examination of the eye in methanol poisoning often shows the pupils to be dilated and unreactive. Visual loss is associated with hyperemia of the optic disc. Blurring of the disc margins, indicative of retinal edema, is observed and, when severe, warns of at least some degree of permanent loss of vision. Atrophy of the disc is observed in some thirty to sixty days.

The physiological explanation for the vulnerability of the eye in methanol intoxication lies in the very high relative oxygen consumption of the retina and the impairment of retinal oxidation and glycolysis by formaldehyde, the normal metabolite of methanol.

therapy

Since the metabolic acidosis and eye injury of methanol poisoning are related to the metabolites of methanol rather than to the alcohol itself, the treatment of methanol ingestion is based upon attempts to impair the metabolism of this compound so that it may be excreted unchanged in the urine. The evidence is that methanol oxidization to formaldehyde is catalyzed by alcohol dehydrogenase, a zinc metalloenzyme which oxidizes other alcohols as well (Li and Vallee, 1969). Ethanol can compete with methanol for active sites of this enzyme, and in fact the enzyme has a greater affinity for the former than the latter. Consequently the therapeutic administration of ethanol permits it to be preferentially oxidized and diminishes the production of methanol metabolites. It is believed by Roe (1955) that sufficient ethanol must be administered to produce a blood level of at least 0.1 percent. Control of acidosis is essential in methanol poisoning, and the use of intravenous bicarbonate has been frequently lifesaving. More recently the value of

hemodialysis or peritoneal dialysis has been emphasized (Cowen, 1964). The relative availability of peritoneal dialysis and rapid determinations of blood methanol and acid-base balance has improved dramatically the prognosis of methanol intoxication (Kane et al., 1968).

ETHANOL

Ethanol (ethyl alcohol, grain alcohol) used in industry is synthesized almost entirely from ethylene. Beverage ethanol is derived from the fermentation of carbohydrates, and the supply for this purpose is not augmented by synthetic ethanol.

While the problems of ethanol intoxication associated with beverage ingestion are well known, industrial exposures to ethanol vapors are of no practical importance. Lester and Greenberg (1951) computed the absorption via the respiratory tract that would be necessary to cause any continuous increase in blood ethanol levels. They concluded that a workman exposed to 1,000 ppm would have to breathe at a rate of 65 L/min. Since a ventilatory rate of 30 L/min. is associated with hard work, the hazard of systemic effects from airborne ethanol is unlikely. At air concentrations of 5,000 to 10,000 ppm, there may be mild transient coughing or irritation of the eyes and upper airway. Concentrations of 20,000 ppm are intolerable. Industrial workers sometimes drink ethanol on hand for manufacturing or other industrial purposes, thus adding to the total dose absorbed.

Ethanol absorption, regardless of the route of administration, may produce very undesirable effects in workers taking disulfiram or exposed occupationally to this compound or thiram.

PROPYL, ISOPROPYL, BUTYL ALCOHOL

Propyl and isopropyl alcohol have no current toxicological importance in industry. Of the butyl alcohols, n-butyl alcohol has been most intensively studied. At concentrations of 100 to 200 ppm there may be irritation of the eyes and upper airways, and the apparently specific formation of minute vacuoles of the cornea has been observed in workers coating raincoats with material containing this solvent (Cogan and Grant, 1945). The other butyl alcohols have similar irritative properties.

PENTYL OR AMYL ALCOHOLS

The pentyl or amyl alcohols ("fusel oil") are irritating and have produced illnesses, some fatal upon ingestion. The toxicological significance in industry of these alcohols and their heavier homologues is small.

ALLYL ALCOHOL

Allyl alcohol (CH_2=CH–CH_2–OH) is a pungent chemical intermediate with potent irritant properties. Absorption through the

skin leads to deep muscle pain, presumably due to spasm. Lacrimation, retro-bulbar pain, photophobia, and blurring of vision may be associated with exposure to vapors, and corneal injury has been described. When this material is used in an open system, exhaust ventilation is essential, and clean-up of spills requires that personal protective devices be used.

ETHYLENE CHLOROHYDRIN

Ethylene chlorohydrin (chemically 2-chloroethyl alcohol) is an extremely toxic compound used for its special solvent properties and as a chemical intermediate. It readily penetrates the skin and most rubber gloves. The mechanism of toxicity is not understood. Several cases have been described in which the fatal outcome was preceded by nausea and vomiting, weakness, and respiratory failure (Bush et al., 1949).

ETHYLENE GLYCOL

Ethylene glycol is the basic constituent of "permanent" antifreeze and many hydraulic fluids. It has a low vapor pressure, and significant air concentrations are not achieved unless the compound is heated or sprayed as a mist. Respiratory exposures or application of the material to the skin are not considered to be of toxicological significance. Intoxication does occur when ethylene glycol is taken by mouth, and an estimated fifty fatalities annually in the United States result from the ingestion of this compound by mistake or as a substitute for beverage ethanol.

toxicity

The mean lethal dose for an adult has been estimated to be about 100 ml. The cause of death in these cases is either central nervous system depression or renal failure related to the formation of oxalic acid, the normal metabolite of the glycol. In most cases the initial symptoms are similar to those of ethanol intoxication, but there may be significant nausea and vomiting, abdominal pain, and respiratory failure. Renal disease is marked by albuminuria and oliguria, and oxalate crystals in the urinary sediment are prominent. Clinical experience suggests that large doses of ethylene glycol lead to death from relatively prompt central nervous system depression, while somewhat smaller or repeated doses, insufficient to cause this depression, result in renal insufficiency.

treatment

The metabolic basis of ethylene glycol poisoning is related to the oxidation of this compound to oxalic acid by alcohol dehydrogenase. Since impairment of this oxidation has therapeutic value, ethanol has been used to compete with glycol for active enzyme sites (Li and Vallee, 1969). Human alcohol dehydrogenase is demonstrated to have an affinity for ethanol some thirty to forty

times that for ethylene glycol. That ethanol administration leads to increased urinary excretion of unchanged glycol and reduction in oxalate production has been shown in monkeys and in at least four patients. Dialysis also has value for the removal of ethylene glycol. Supportive measures often must include vigorous treatment with sodium bicarbonate to control severe and persistent metabolic acidosis.

DIETHYLENE GLYCOL

Diethylene glycol is a similar compound but with little industrial hazard. From the toxicological point of view it is significant mainly in that over 100 deaths occurred in the United States in the late 1930s as a result of the ingestion of an elixir of sulfanilamide containing 72 percent glycol. Fatal cases showed progressive renal failure with death in less than eight days after the onset of anuria.

OTHER GLYCOLS

Other glycols such as propylene glycol and the polyethylene glycols are not considered to be of toxicological importance in industry. Their metabolites do not include oxalates, formic acid, or formaldehyde.

ALKYL DERIVATIVES OF ETHYLENE GLYCOL

The principal alkyl derivatives of ethylene glycol are the monoethyl ether (Cellosolve), the monomethyl ether (methyl Cellosolve) and the butyl ether (butyl Cellosolve). They are important solvents for industrial coatings and inks. The three compounds are considered to have similar harmful properties with toxicity increasing in this order. All can be absorbed via the skin, lungs, or gastrointestinal tract. Acute poisoning usually affects the central nervous system and the kidneys. With less intense and more prolonged exposure, involvement of the hematopoietic system is also observed. Anemia, which resolves on cessation of exposure, is reported. In some situations the anemia is described as macrocytic with a predominance of immature leucocytes. The hemolytic anemia which occurs in experimental animals exposed to butyl Cellosolve has not been reported in man. The Cellosolves are all irritating to the skin and mucous membranes. The effects of these glycol derivatives upon the central nervous system include headache, drowsiness, weakness, slurred speech, recrudescent stuttering, staggering gait, tremor, and blurred vision (Zavon, 1963). Changes of personality are often noted first by the family of the affected individual. These changes are such that the patient, in the absence of an accurate occupational history, may be treated for schizophrenia or narcolepsy.

In acute poisoning with the ethylene glycol monoalkyl ethers,

there is frequently evidence of renal injury: albuminuria and hematuria. The clinical nature of this renal disorder is not well established, but it is unrelated to oxalates.

A similar series of monoalkyl ethers of diethylene glycol form the series of solvents known in industry as Carbitols. Diethylene glycol monoethyl ether (Carbitol), diethylene glycol monomethyl ether (methyl Carbitol), and diethylene glycol monobutyl ether (butyl Carbitol) have not been associated with industrial intoxication.

DIOXANE

Dioxane, a valuable solvent for industrial coatings and a dehydrating agent in the preparation of histological slides, can be inhaled in amounts sufficient to cause serious systemic intoxication. Its warning properties are poor. Consequently injury may become apparent hours after termination of an exposure which had been erroneously considered to be negligible. Acute exposures, as of technicians in a histology laboratory, may lead to headache, nausea, vomiting, and irritation of the eyes. Five fatalities have been reported in the literature (Barber, 1934). While the quantitative aspects of the dioxane exposure were unclear, post-mortem studies in these cases demonstrated prominent renal and hepatic injury. The cause of death was considered to be hemorrhagic nephritis. Animal experiments confirm the nephro- and hepatotoxicity of dioxane.

KETONES AND ETHERS • 6

The ketones, used widely as solvents, have no currently recognized general toxicological properties. The principal exceptions are certain halogenated or unsaturated ketones with special limited uses. The ketones can be irritating to the eyes and mucous membranes. Industrial limits of exposure are based primarily on levels in air which do not produce irritation or an unpleasant sensory response. At very high levels it is possible to produce narcotic effects with simple ketones.

Industrial experience with acetone (dimethyl ketone) has been extensive. Careful industrial hygiene and occupational medical studies on literally hundreds of workers exposed to levels of 1,000 to 2,000 ppm for many years have confirmed the relative safety of this compound. Methyl ethyl ketone (MEK) is more irritating to the eyes and upper airway than is acetone; however there has been no industrial evidence of organotoxicity. Nausea, vomiting, headache, and other subjective complaints may occur at high levels of exposure. The experience with methyl isobutyl ketone (MIBK) has been similar. Wagoner (1973) has discussed an industrial epidemic of peripheral neuropathy involving some fifty workers exposed to methyl butyl ketone (MBK) in a print shop. This phenomenon had not been associated with previous exposures of similar magnitude to methyl ethyl ketone and methyl isobutyl ketone. The mechanisms of neurological disease production remain to be identified as do many of the clinical and epidemiological aspects of this intoxication.

Cyclohexanone and its analogues are not of toxic importance, although they may cause transient irritation. Certain unsaturated ketones have important biological properties.

Ethers, well known for their narcotic properties and ability to act as fat solvents upon the skin, have no general industrial toxicological properties of practical importance. The principal exception is that presented by bis-chloromethylether (BCME) and possibly by chloromethylether (CME) which, however, is almost always contaminated with the former compound. Bis-chloromethylether is a biologically active alkylating agent with clearly identified carcinogenic properties for mucosa, skin, and lungs. Epidemiological studies in industry (Figueroa, et al., 1973; Thiess, et al., 1973; Nelson, 1973) have demonstrated that BCME is a potent occupational carcinogen, identified with the induction of "oat cell" ("small cell") carcinoma of the lung. The investigations of Thiess revealed that, of eighteen persons employed in a technical

research center, six died of carcinoma of the lung. In addition two of fifty production workers, protected by a "closed system" and fresh air masks, also died of lung cancer during the same six-year period. The evidence for the extreme carcinogenic potency of BCME and the fact that airborne levels of this compound are measurable when formaldehyde and hydrochloric acid react suggest that histological technicians who conduct operations in which this reaction may occur should be protected by suitable ventilation.

AROMATIC NITRO AND AMINO COMPOUNDS • 7

Aromatic nitro and amino compounds comprise a varied group of substances which are fundamental to industries producing explosives, pharmaceuticals, rubber chemicals, and "aniline" or "coal tar" dyes. Other compounds of the group are intermediates in the synthesis of pesticides, plastics, and paints. While certain members of the nitro ($-NO_2$) and amino ($-NH_2$) aromatic group have relatively specific toxic effects, it is generally true that there are properties which are characteristic of the group. Many of these compounds produce methemoglobin, some are bladder carcinogens, and others uncouple oxidation from phosphorylation. There are unusually potent skin sensitizers in the group. Liquid nitro- and amino-aromatics are readily absorbed through the intact skin.

TOXICITY

Methemoglobinemia is considered to be the outstanding acute reaction to most nitro and amino aromatic compounds (Bodansky, 1951). In cases of chemical methemoglobinemia, it is not clear whether or not all manifestations in man reflect hypoxemia exclusively and that the chemical compound implicated (e.g., aniline) is without specific direct pharmacologic influence on body systems. The presence of severe methemoglobinemia tends to obscure other possible acute manifestations reflecting direct toxicity. It is probable that chemically active compounds of this group do have direct organ effects, but it is difficult to provide convincing demonstrations.

In biochemical terms methemoglobin is the chemical analogue of hemoglobin in which the iron of the heme moiety has become oxidized from the normal Fe^{++} (ferrous) state to the abnormal Fe^{+++} (ferric state). Oxygen bound to methemoglobin is so firmly attached that it is not available to tissues and, in fact, can be separated from the carrier pigment only by rather drastic nonphysiological means. Consequently methemoglobin is not an oxygen-transporting pigment. Tissue hypoxia is the consequence of hemoglobin oxidation, not oxygenation, to Fe^{+++}. Methemoglobin also interferes with the release of oxygen from normal hemoglobin so that hypoxia is more severe than the methemoglobin levels might suggest (Darling and Roughton, 1942).

Organic and inorganic nitrites, organic nitrates, and quinones form methemoglobin directly; inorganic nitrates on ingestion may

produce methemoglobin through the action of intestinal bacteria which yield nitrites. In most cases it is probable that metabolites of the aryl nitro and amino compounds are the proximate cause of blood pigment oxidation. Phenylhydroxylamines and nitroso compounds are prime possibilities as the methemogoblin-producing metabolites. Clinical observations indicate that nitro compounds are associated with a more insidious onset of methemoglobinemia and a more prolonged course than would be the case with the corresponding amino compounds. These observations may reflect a somewhat slower conversion of the nitro compounds into the actual methemoglobin producer.

Methemoglobin is normally present in man in a low concentration. An equilibrium exists between hemoglobin and methemoglobin, the latter being continuously reduced by an intracellular methemoglobin reductase known as diaphorase (Smith, 1969). Glycolysis is adequate to drive this mechanism at a rate sufficient to handle normal pigment loads. With massive chemical exposure, this mechanism is inadequate to handle the load of abnormal oxidized pigment, and clinical cyanosis becomes evident. An auxiliary reducing mechanism can participate in the reduction of methemoglobin when methylene blue is administered therapeutically. The precise biochemical nature of each step in this reduction is not yet clear, but the evidence is good that methylene blue may be of great value in the clinical treatment of methemoglobinemia (Wuertz et al., 1964). Industrial experience with methylene blue has been limited, a fact which is probably related to existing reports that methylene blue is itself a methemoglobin producer. More recent interpretations support the opinion that methylene blue does not produce methemoglobin in most laboratory animals and probably not in man.

Aniline, nitrobenzene, and indeed most of their homologues (e.g., dinitrobenzene, nitroaniline) generate methemoglobin. Many of these compounds penetrate the skin, and vapors or dusts are absorbed rapidly in the lungs. The onset of cyanosis is usually insidious, and the time required is a function of the absorption rate and the specific compound absorbed. Nitrobenzene and other nitro compounds generate methemoglobin more slowly, but cyanosis is more persistant.

The onset of cyanosis is often first noted at the lips ("blue lip") and ears. The color is more violet, lilac, or "huckleberry pie" than the cyanosis associated with unoxygenated normal hemoglobin. Symptoms may be absent, although euphoria, flushed facies, and a headache are common. Cyanosis is usually detectable when the proportion of converted hemoglobin approximates 15 percent.

Methemoglobin levels to 40 percent may exist without symptoms other than a sense of well-being. At higher levels headache may become severe; weakness, ataxia, and lightheadedness occur. With increasing concentrations of methemoglobin, dyspnea, tachycardia, and alarming cyanosis are noted. Even at conversion levels approximating 75 percent, however, recovery without specific therapy has been the rule.

treatment

In most cases of methemoglobinemia the most useful therapeutic procedure is simply a prompt and thorough cleansing of the patient with soap and warm water with special attention to the hair and nails. Contaminated footwear must be discarded. There are numerous examples of a recurrence of "blue lip" after an apparently cured patient puts on clean clothing and steps into his old shoes, a source of absorbable aniline or nitrobenzene. Bed rest is indicated. The headache is often relieved promptly by the administration of oxygen, although this procedure has no effect on methemoglobin reduction.

That these conservative procedures need to be supplemented with active therapeutic measures is not clear. Better industrial practice suggests, however, that methylene blue is indicated when methemoglobin levels rise in excess of 40 percent. The usual dose of the dye is 1 to 2 mg/kg of body weight as a 1 percent solution in saline. Ascorbic acid, a reducing agent, has also been used, but it appears to be less effective than methylene blue. From time to time the possibility of exchange transfusions has been raised. This step is seldom, if ever, considered necessary.

Recovery is usually rapid, and spontaneous disappearance of cyanosis may occur in hours. With high levels of methemoglobin and when the agent involved is a nitro compound, twenty-four or more hours may be required. When recovery is slow, the physician must consider the possibility that compounds are still being absorbed from the skin.

The management of methemoglobinemia is facilitated by prompt accurate determinations of the oxidized pigment in the blood. Spectrophotometric procedures are readily available. Methemoglobinemia has been associated from time to time with reports of a hemolytic anemia. Heinz bodies, small refractile granules in erythrocytes, have been attributed to exposure to aromatic amines and nitro compounds and to nitrate and nitrate esters (Hanley and Mauer, 1961).

Hepatic injury related to aryl amino compounds has been rare. There are reports of acute hepatic disorders in benzidene workers, but effects in this population are presumably due to heavy expo-

sures. Nitro compounds of the dinitrobenzene and trinitrotoluene (TNT) type have a history of prominent hepatotoxic effects often associated with an aplastic anemia. The data come to a large degree from the British munitions industry in both World Wars and to a lesser extent from similar American sources. Both chemicals are readily absorbed through the skin, especially when the skin is exposed and wet with sweat. Hepatic injury is manifested by jaundice, which often is demonstrable only in the conjunctivae since the skin of workers with this degree of exposure may already be dyed yellow from the compounds in question. Unfortunately this clinical manifestation is a late sign of injury and is not satisfactory in the prevention of acute yellow atrophy. Earlier symptoms are not sufficiently specific to be very useful in prevention.

McConnell and Flinn (1946) reported twenty-two cases of fatal TNT poisoning which occurred in American industry in World War II. Of these, thirteen were due to aplastic anemia, eight were due to acute yellow atrophy of the liver, and one was due to hepatitis followed by fatal aplastic anemia. The number of nonfatal cases during the same period was not reported, but recovery from either toxic hepatitis or toxic aplastic anemia is rare. It is very probable that TNT-related disease was much more common than these figures suggest, especially during World War I. There is reason to believe that a somewhat better health record in the TNT industry during World War II may be due to the fact that tetranitromethane, a toxic and irritating impurity of crude TNT, was removed during that period (Sievers et al., 1947).

DINITROBENZENE

Dinitrobenzene is some twenty times as potent a methemoglobin producer as is TNT; consequently, the appearance of cyanosis provides warning of exposure to this potent hepatotoxin.

PICRIC ACID AND TETRYL

Other aromatic nitro explosives, picric acid (trinitrophenol) and tetryl (methyltetranitroaniline) do not pose major industrial health hazards except during very high exposures as encountered in wartime. Tetryl is highly irritating to the skin and mucous membranes and may cause severe upper respiratory tract irritation with coughing and epistaxis. The compound stains the skin and hair yellow. Picric acid produces a similar contact dermatitis and staining. There is evidence that heavy exposures to tetryl may cause liver damage (Hardy and Maloof, 1950).

TRIMETHYLENE-TRINITRAMINE

Trimethylenetrinitramine, called cyclonite or RDX, a related heterocyclic compound, is a military high explosive. It has been found to cause convulsions in men working under poor conditions of hygiene (Barsotti and Crotti, 1949). Typical epileptiform seizures

may be preceded by a few days of irritability, insomnia, or restlessness. No sequelae have been observed following the cessation of exposure. Primary and sensitizing dermatitis may also be caused by RDX or, more likely, by impurities or chemical intermediates associated with its production. RDX does not induce methemoglobinemia or nitrate effects.

DINITROCHLOROBENZENES

The dinitrochlorobenzenes are almost universal skin sensitizers; a minute contact will sensitize approximately three-fourths of all persons tested. The reaction may vary from a small area of pruritic vesiculopapular eruption to a generalized exfoliative dermatitis. The 2,4-isomer is used in experimental sensitizations; presumably it combines with lysine in cutaneous proteins to form a complete antigen.

DINITROPHENOLS AND DINITRO-O-CRESOL

The dinitrophenols and dinitro-o-cresol, referred to as DNOC, which have uses as pesticides, are distinctive from the toxicological point of view in that they are compounds with marked effects upon energy-producing metabolic mechanisms. Upon absorption, these compounds uncouple oxidation from phosphorylation. Energy made available by oxidation is not converted into active phosphate but is expended in raising body temperature. Cataracts may occur in cases in which extreme elevations of body temperature are achieved, and fatal hyperpyrexia has been reported (Bidstrup and Payne, 1951).

aniline tumor of the bladder, industrial illness

The so-called aniline tumor of the bladder, is currently believed to be related to absorption of any one of the following four aromatic compounds: 2-naphthylamine (β-naphthylamine), 4-aminodiphenyl (xenylamine), 4-nitrodiphenyl, and 4,4-diaminodiphenyl (benzidine). The disease was first reported in the German dye industry by the surgeon Rehn, who, in 1895, reported four dye workers with tumors of the bladder. He concluded that vapors of aniline, used in the production of the dye fuchsin, were responsible. Not until 1934 did the first American report appear in the form of a number of articles prepared by a group of physicians associated with E. I. duPont de Nemours Company. Gehrmann's contribution to the symposium described cystoscopic examination of 587 men and the discovery of twenty-seven positive cases (Ferguson et al., 1934). Sixteen other cases were found in which there were hemorrhagic areas of the bladder. The age of men affected ranged from thirty to sixty years, and the duration of exposure from four to eighteen years. Except for two α-naphthylamine workers, all the men had been exposed to either

β-naphthylamine or benzidine. No tumors were detected in workers exposed exclusively to aniline. The evidence is convincing that tumors in the α-naphthylamine workers were actually due to contamination by the β-isomer.

The fact that many aromatic amines and related compounds are present in those segments of the chemical industry in which occupational bladder tumors have arisen has produced speculation as to relative toxicities of compounds, the proximate carcinogen, and the carcinogenetic mechanism. As far as is known, only those compounds listed in the previous paragraph produce bladder tumors in man. Additional data from studies in dogs indicate the carcinogenic potential of other aromatic amines: 2-acetylaminofluorene, N:N-dimethyl-4-aminoazobenzene, and 4-amino-3:2'-azotoluene. It must be presumed that these compounds are carcinogenic in man as well; he has been protected by limited industrial exposure. The accumulating evidence supports the view that these compounds themselves are not carcinogenic, for they fail to produce tumors when implanted directly in the bladder of experimental animals. Man and dogs appear to be species with the necessary biochemical mechanisms for transforming these compounds into the proximate carcinogen (Troll and Belman, 1967). Carcinogenic metabolites have been isolated in the urine of dogs. This material can induce tumors in the rat bladder, whereas the parent amine cannot, either by direct implantation or by parenteral administration.

Occupational tumors of the bladder follow a long latent period averaging about eighteen years, with reported extremes of one and forty-eight years. Durations of exposure have also varied widely from less than a year to many years. Age is not clearly a factor in the development of disease. Once initiated, the course of occupational bladder tumors is not dissimilar to bladder tumors arising in the general population. The tumors may present as a benign papilloma, a simple noninvasive, nonmetastasizing growth on the bladder wall. Other tumors may first be found as invasive carcinomata; there are all patterns of intermediate categories. In all instances there is a tendency to recurrence and complications from hemorrhage and infection. Whether the tumor is a benign papilloma or a metastasizing carcinoma appears to have no relationship to characteristics of the exposure or the worker. Primary tumors in the renal pelvis and ureters have also been observed, but there is no evidence that these carcinogenic aromatic compounds produce tumors outside the urinary system.

therapy and control

Treatment is surgical. In a number of cases the bladder has been excised and the ureters have been connected to an ileal

bladder. Medical surveillance is based upon exfoliative cytological examinations of urinary sediment and on periodic cystoscopy. In men who are known to have been exposed to bladder carcinogens there does not appear to be an alternative to these procedures. The obvious solution in the case of unexposed workers is the enclosure and control of relevant industrial processes. In some jurisdictions the production of β-naphthylamine has been made illegal.

TOLUIDINES AND CHLORTOLUIDINES

From time to time hematuria may be observed in men handling toluidines and chlortoluidines. There may be a hemorrhagic cystitis with painful and frequent micturition. This acute problem is of no long-term significance and clears promptly on cessation of toxic exposure. If hematuria persists, the question of other pathological urinary tract phenomena must be considered. The cystitis related to these aniline derivatives has no relationship to carcinogenic amine-related processes.

PARA-PHENYLENEDIAME AND PARA-AMINOPHENOL

Para-phenylenediame and para-aminophenol are dye intermediates, which, when applied to furs and properly treated, give a brown or black color. These compounds are potent skin and respiratory allergens and can produce severe bronchial asthma among workers in the fur-dyeing industry. Dermatitis from properly finished fur is rare, however, since these dyes are well fixed to the hairs and do not cause reactions even in highly sensitized persons.

DIMETHYL-NITROSAMINE

Histories of two cases of poisoning from dimethylnitrosamine were picked up by Hamilton in the course of a survey of a large automobile factory (Hamilton and Hardy, 1949, p. 301). Apparently the action of the poison was on the liver, producing cirrhosis with jaundice and ascites. The first subject was violently ill but pulled through, the second was less affected and was recovering when he developed an infection from the paracentesis and died. The liver was cirrhotic, with areas of regeneration. The hepatotoxic action has been confirmed in animal studies reported by Barnes and Magee (1954). Elkins (1959 p. 175) describes dimethylnitrosamine as a useful solvent because it is miscible with water, methylene chloride, and vegetable oils. However, in view of the evidence that this compound is a carcinogen, exposure should be reduced to a minimum.

ESTERS • 8

Esters are formed when an organic grouping, simple or complex, replaces an acidic hydrogen atom in an organic or inorganic acid. They are used extensively in the plastics industry, either as resins or as plasticizers, and as solvents for lacquers. Esters of inorganic acids may have prominent corrosive or pharmacological properties, and indeed this group may be considered to include the clearly toxic organophosphate insecticides. Although there are notable exceptions to the rule, esters of organic acids are generally of low toxicity. Nonspecific irritative effects are commonly associated with the presence of a double bond in these esters which, if saturated, would be essentially harmless. Conjunctivitis and upper airway symptoms may occur and pulmonary edema is possible in cases of massive over-exposure. These irritating unsaturated esters include the acrylates, methacrylates, and crotonates, and various vinyl and allyl esters.

BIOLOGICAL EFFECT OF INDUSTRIALLY USED ESTERS

With the exception of certain phosphate esters used as plasticizers, those esters used as resins and plasticizers are physiologically inert in the industrial environment. This group includes the succinate, adipate, azelate, sebacate, citrate, and phthalate plasticizers. Minor degrees of epithelial irritation may follow highly unusual or intentionally created exposure conditions in which vapors of heated material are inhaled or in which skin exposures are prolonged. Even then, observed manifestations may be due to impurities, decomposition products, or physical aspects of the exposure situation. Reports of sensitizing reactions are rare and do not always suggest unequivocal etiologies. Inhalation of dusts has produced no specific pulmonary reaction.

ALIPHATIC ESTERS

The aliphatic esters used as lacquer solvents, primarily ethyl acetate and butyl acetate, have narcotic properties which are less prominent than those associated with the chlorinated hydrocarbons. The ester solvents are also powerful defatting agents when applied to the skin and produce a nonspecific drying, cracking, and increased susceptibility to infection. Sensitization is rarely if ever encountered. Solvent ester vapors are generally irritating to the conjunctivae and mucous membranes of the upper airway but leave no residual effects. There have been rare reports in the literature of visceral injury, effects upon the bone marrow, and nervous symptoms. Careful consideration of all exposure and diagnostic data in these cases almost always suggest that the

esters mentioned were not necessarily responsible for the observations reported. As a group the ester lacquer solvents comprise a category of compounds that have relatively insignificant toxic properties.

HALOGENATED ACID ESTERS

A small number of halogenated acid esters are potent lachrymators and vesicants and have the potential for producing pulmonary edema. Compounds in this category are important organic intermediates and include ethyl chloroformate, ethyl chloroacetate, and related bromo- and iodo-compounds. Several of these materials have been used as chemical warfare agents. There is no evidence that they produce chronic disease, but fatalities have occurred from acute pulmonary edema. The highly hazardous character of these compounds appears to be related to the high reactivity of the halogen atom and not to the fact that they are esters.

ALKYL ESTERS OF SULFURIC ACID

Alkyl esters of sulfuric acid, primarily dimethyl and diethyl sulfate, are important alkylating agents in industrial organic synthesis. These are intensely irritating substances, producing inflammation of the eyes and upper airway, vesication of the skin, and pulmonary edema. Dimethyl sulfate was used in World War I as an irritant and vesicant. Dimethyl sufate is extremely hazardous because of its deficient warning properties and the delayed deep lung reaction. Two cases reported by Littler and McConnell (1955) are typical of those which occur. In one case a young chemist splashed dimethyl sulfate on his skin and clothing but immediately flooded the contaminated areas with water, diluted sodium hydroxide, and ammonia. There were no immediate symptoms; however, bronchospasm, rales, tachycardia, and marked swelling of the eyes occurred about four hours after the incident. Thirteen hours after exposure, large vesicles appeared upon the skin. There was a severe cough with sputum containing shreds of necrotic tracheal mucosa. Subcutaneous emphysema indicated perforation of the trachea or bronchi. The second man, exposed probably only to vapors of dimethyl sulfate, developed pulmonary edema twelve hours after exposure, and swelling of the face and hands, disturbance of visual fields, and analgesia, which has been commonly reported in others. Both men recovered without residual effects, although some scarring of the skin resulted. Cases of this sort were often fatal prior to the availability of antibiotics for control of infection in areas of skin necrosis. These cases illustrate the potent toxic properties of dimethyl sulfate vapor, the latent period be-

tween exposure and illness, and the serious complications which may ensue.

control

Clinical manifestations due to methylchlorosulfonate, ethyl chlorosulfonate, and methyl-p-toluene sulfonate are similar to those associated with dimethyl sulfate, and similar precautions are warranted. Contaminated areas should be entered only by trained personnel with impervious clothing and air-supplied respirators. Contact of these compounds with the skin or eyes is an indication for rapid and prolonged irrigation of the area with large volumes of water. Decontamination of floors and equipment may be effected by flushing with dilute alkali or ammonia.

PHOSPHATE ESTERS

Specific phosphate esters comprise a major category of organic insecticides with important associated occupational medical implications. Other phosphate and phosphite esters, lacking significant insecticidal properties, are widely used as plasticizers and as gasoline additives. Included in this group are tri-o-cresyl phosphate, triphenyl phosphate, tri-2-ethylhexyl phosphate, and 2-ethylhexyl diphenyl phosphate. As plasticizers, these compounds offer the additional property of flame retardancy and are used widely in vinyl and cellulosic formulations. Triphenyl phosphite is a color stabilizer in alkyd resins and an additive to epoxy plastics. Many phosphate esters used as plasticizers may be added to gasolines to control pre-ignition. Tricresyl phosphate is often used for this purpose, and advertising stressing "TCP" is not unknown.

While some of these plasticizer and fuel additive phosphorus-containing esters do have weak cholinesterase-inhibiting properties, clinical effects associated with disturbances of transsynaptic transmission are not important. Of great significance, however, is the fact that some of these compounds induce delayed neurological effects marked by destruction of axons and demyelination in the peripheral nerves and spinal cord. Experimentally one can demonstrate that certain cholinesterase-inhibiting insecticides are also delayed neurotoxins; however this can usually be shown only when the animal is protected from prompt lethal cholinergic effects with prophylactic atropine and oximes. There does not appear to be a correlation, positive or negative, between cholinesterase inhibition and delayed neurotoxicity.

Tri-o-cresyl phosphate (TOCP) and phosphite and triphenyl phosphate and phosphite are delayed neurotoxins lacking potent anti-cholinesterase properties. There are other phosphorus esters

in this category, and more will undoubtedly be developed. Health officers responsible for the surveillance of men handling phosphorus esters should insist upon accurate information describing the presence or absence of associated acute or delayed neurotoxic properties. There is species-to-species difference in susceptibility to delayed neurotoxic effects. Accordingly toxicological data must be evaluated critically, and information derived from rodents exclusively should be regarded as insufficient.

reports of illness

Although clinical cases of delayed neurotoxicity following industrial exposures to several aryl phosphates have been described, the vast majority of cases has followed the ingestion of food or beverages which had been previously contaminated with tricresyl phosphate esters containing the ortho isomer. The United States epidemic occurred in 1930 during Prohibition and produced as many as 15,000 cases of permanent paralysis, often slight, and a small number of deaths. The epidemic of paralytic disease was due to the ingestion of Jamaica ginger extract ("jake") which had become contaminated with tri-o-cresyl phosphate. "Jake" was an alcoholic preparation sold as a flavoring but used as a substitute for conventional alcoholic beverages, especially by heavy drinkers and homeless male drifters (Kiely and Rich, 1932). There are various theories, none proved, giving explanations for the contamination in communities across the country.

Similar paralytic disease has followed the ingestion of this ester in an abortifacient, in several cooking oil epidemics, and in illegal alcoholic beverages. The most recent epidemic occurred in Morroco in 1959 and involved 10,000 people who used olive oil adulterated with jet engine lubricating oil containing TOCP (Albertini et al., 1959). Of these some 10 to 15 percent remain permanently crippled and unable to resume their previous employment.

In each of these situations, the clinical picture has been consistent. There may be a prompt transient gastrointestinal disturbance with nausea, vomiting, and diarrhea lasting a few hours to a few days. The onset of neurological disease is delayed for three days to a month and is marked by sharp, cramping pains in the legs, numbness and tingling in the feet, and, subsequently, weakness of the legs and foot drop. The upper extremities may become involved days later. The effects are symmetrical, the cranial nerves are rarely involved, and persistent sensory manifestations are held to be lacking in some, but not all, epidemics. The flaccid paralysis is associated with wasting of the calves and small muscles of the hands. Upper motor neuron effects, which may develop over the course of months and bring spasticity, suggest an unfavorable

prognosis as far as complete recovery is concerned. In milder cases recovery may appear to be complete, but residual effects are often demonstrable by detailed neurological examination. Many cases of apparent full recovery may be to a large extent examples of effective adaptation to permanent motor loss.

NITRATES

The nitrates are esters of alcohols and nitric acid. Their most common use has been in military and mining explosives. Glyceryl trinitrate (nitroglycerin) is used as the active component of dynamite and as a coronary vasodilator in clinical medicine.

Industrial experience with aliphatic nitrates is associated primarily with the explosives industry, which has produced glyceryl trinitrate (nitroglycerin) and ethylene glycol dinitrate for many years. These compounds are the principal sensitizing ingredients in dynamite; they are absorbed in a "dope" of oxidizing salts and various inert fillers such as wood fibers or corn starch. Small amounts of other nitrogen-containing compounds, such as dinitrotoluene, may be added. Ethylene glycol dinitrate, more volatile than the original glyceryl nitrate of early dynamites, is added to this latter compound to increase the stability of the product and lower its freezing point for low-temperature mining applications. Both nitrate compounds pass readily through the skin and are sufficiently volatile to produce symptoms in a short period. The effects of absorption are observed in explosives makers, dynamite packagers and fillers, miners, and men handling cordite.

toxic effects

The principal biological properties of the nitrates are their ability to oxidize heme iron to the ferric state to produce methemoglobinemia and to cause vasodilatation. Vasodilatation is associated with hypotension, intense throbbing headache, flushing, palpitation, and, less frequently, nausea, vomiting, or abdominal distress. The interval between exposure and the onset of symptoms and the duration of "nitrate effect" varies with the individual compounds. Glyceryl trinitrate typically gives a prompt response of brief duration; other agents are slower in producing effects. There is variability in the ability of the various nitrates to produce methemoglobin: ethylene glycol dinitrate is very active, glyceryl nitrate is less so, and ethyl nitrate is weakly active.

Most nitrates produce Heinz bodies, small round erythrocyte inclusions commonly associated with methemoglobin and a history of exposure to inorganic nitrates, organic nitrates, and aromatic nitro- and amino-compounds (Hanley and Mauer, 1961). Red cells containing Heinz bodies have relatively short life spans and appear to be preferentially sequestered by the spleen. Their persis-

tence in the peripheral blood is usually of longer duration, however, than that of associated methemoglobinemia. The current view is that Heinz bodies are composed of insoluble degradation products of hemoglobin which precipitate.

GLYCERYL TRINITRATE AND ETHYLENE GLYCOL DINITRATE

harmful effects

These compounds produce hypotension, tachycardia, palpitation, nausea, vomiting, and a characteristic headache or "powder head." The headache usually commences as a feeling of warmth or fullness in the head and develops into a throbbing sensation which progresses from the forehead to the occiput or the back of the neck. Although there is wide variability between individuals, most powder workers develop a tolerance to the effects of these nitrates and have no symptoms as long as exposure is maintained. The tolerance may be lost over a weekend or holiday, in which case the return to work is marked by a return of symptoms. There are many reports of workers who carried small pieces of dynamite in their hatbands or who placed pieces around their homes so as to maintain exposure and tolerance. Such reports also describe, however, the violent headaches experienced by persons not in the explosives industry who entered these homes as visitors and thereby became exposed to an acute dose of nitrate. A physiological explanation for the powder headache may be related to dilatation of the cerebral vasculature and drop in cerebrospinal fluid pressure under the influence of these compounds. Temporary relief of headache can be obtained with vasopressors or ergotamine tartrate. More intense exposure has been associated with hypotension, confusion, and methemoglobinemia. The concurrent absorption of beverage alcohol has been noted on many occasions to intensify the confusion, and frankly maniacal phenomena have been described.

There is evidence that the cardiovascular effects induced by glyceryl trinitrate and ethylene glycol dinitrate may be associated with sudden death in explosives workers—often on Monday morning (referred to as Monday morning death), on return from a holiday, or from a weekend (Carmichael and Lieben, 1963). The clinical diagnosis has been acute myocardial infarction, often, but not always, with little evidence of antecedent coronary artery disease or of coronary occlusion. Critical review of the literature suggests that some three-fourths of sudden death in these workers occurs after one or two days' absence from exposure. Although the epidemiological evidence for a causal association between exposure and sudden death is impressive—though circumstantial—there are several theories which might provide an explanation for the observations. It may be that coronary artery vasospasm

follows the vasodilatation of acute re-exposure without tolerance or that vasodilatation and a drop in blood pressure causes insufficient return of blood to the right heart and cardiovascular collapse. These views are favored in the literature when no anatomical explanation for death is found at post-mortem. An additional theory is based upon the view that chronic exposure to vasodilating drugs may impair nutrient arterioles in the walls of coronary arteries causing the deposition of hyaline connective tissue. While there is experimental evidence for this interpretation, the explanation for the epidemiological observations is not yet clearly established.

PENTAERYTHRITOL TETRANITRATE

Pentaerythritol tetranitrate is used as a detonator or booster or can be combined with trinitrotoluene. The nitrate effects from PETN are much less apparent than those associated with the use of nitroglycerin or ethylene glycol dinitrate although there may be a contact dermatitis.

ALKYL NITRITES

The alkyl nitrites such as amyl nitrite produce vasodilatation, tachycardia, and hypotension which may lead to collapse and shock. A throbbing headache is characteristic, and tolerance is developed with repeated exposure. Methemoglobinemia may occur, but Heinz bodies are not known to be present. For the most part it is apparent that the effects of alkyl nitrates and nitrites are similar.

ALIPHATIC NITRO COMPOUNDS

Aliphatic nitro compounds, not esters, do not cause nitrate effects but can induce methemoglobinemia. Dyspnea, cough, and dizziness in men handling crude TNT has been attributed to tetranitromethane, an impurity, with prominent irritating properties. Other aliphatic nitro compounds are also irritants. The chlorinated aliphatic nitro compounds can be extremely irritating, and trichloronitromethane (chloropicrin) has been used as a military lacrimator which produces coughing, nausea, vomiting, and pulmonary edema.

CARBON DISULFIDE • 9

Carbon disulfide (CS_2) is said to have been first discovered by Lampadius of Freiburg in 1796. It was recommended as a remedy for a great variety of diseases and was actually used in medicine, more or less, during the following half century. It has been used as an insecticide and in the production of viscose rayon. It is a solvent for waxes, resins, gums, and rubber. For many years it played a very important part in the rubber industry in European countries, somewhat less in England and much less in the United States. In rubber manufacture the crude latex must be made into an elastic, heat-resistant solid and this is done by incorporating sulfur, a process known as vulcanizing. It may be accomplished by adding flowers of sulfur to the mass which is then subjected to heat and pressure. This is known as the "heat cure." Or it may be done by exposing rubber to the action of sulfur chloride either in vapor form or by dipping it into the liquid, or by painting. The carrier or solvent for sulfur chloride usually was carbon disulfide. American manufacturers always have preferred the heat cure for rubber, while Europeans preferred the so-called cold or acid cure with carbon disulfide. It is this last compound that gave to European rubber manufacture a very bad reputation, and the older literature is full of reports of carbon disulfide poisoning in rubber workers. When the process of making an artificial silk called viscose rayon was worked out in Switzerland, France, and England, reports began to come from abroad describing cases of carbon disulfide poisoning in this new industry. In the production of viscose rayon, the starting point is cellulose from wood pulp or cotton linters, which is treated with an alkali to form flake-like "white crumbs," alkali cellulose. This is changed to an orange-yellow, rubbery mass, known as cellulose xanthate by being treated with carbon disulfide in revolving "churns," or "barattes," or "tumbling barrels." From the churns the xanthate goes to viscose mixing machines. The most severe exposure to fumes of CS_2 takes place in the churn room, from leaking pipes and churns, from discharging the churns and scraping out the xanthate that sticks to the walls, and from conveying the xanthate to the viscose mixers and dumping it.

A lesser exposure occurs in the spinning process. The viscose, a thick syrup which is sodium-cellulose-xanthogenate, comes from the mixers and is forced through spinnerets of different degrees of fineness according to the weight of the yarn desired, into the spinning bath of sulfuric acid, sulphates, and other chemicals.

Here the syrup coagulates and decomposes, releasing pure cellulose which is drawn out as a thread and wound on bobbins. There is a lesser production of CS_2 fumes caused by the "ripening" of the cellulose xanthate in the spinning bath with the formation and escape of H_2S and CS_2. Poisoning from the latter is not so frequent nor so severe as in the churn room. Since the recognition of carbon disulfide poisoning as a compensible occupational disease, these processes have been elaborately safeguarded by ventilation systems and routine air analyses are made to check on the efficiency of these systems.

WORKER ILLNESS

A series of reports are quoted by Hamilton and Hardy (1949, pp. 398–408). Carbon disulfide was recognized as an industrial poison by the French almost one hundred years before psychiatrists in the United States were willing to do so. Payen, who first described its action in 1851, was followed by Delpech in 1856, the latter describing twenty-four cases in rubber workers and also experimental poisoning in animals. Constansoux and Heim (1910) gave a detailed picture of CS_2 poisoning in French rubber workers, with loss of appetite, dyspepsia, disturbance of vision, sensory disturbances, and sexual impotence. Two very important studies came from Germany: Laudenheimer published the medical histories of no less than fifty patients with carbon disulfide insanity. The early symptoms consisted of headache, dizziness, increasing sense of weariness, loss of strength, transient excitement, and slight delirium, very like alcoholic intoxication. Later came deep depression and loss of memory, increasing indifference, and apathy. This might change suddenly to acute mania or delusions of persecution with hallucinations. Such cases usually developed early, during the victim's first months of work. Some ended in recovery, others in incurable dementia.

Koester described a slower form, usually a toxic polyneuritis, with paralysis and atrophy. He believed carbon disulfide poisoning to be as varied in its manifestations as poisoning from lead. Probably because of this and because so many of the victims were young girls, the French, led by Pierre Marie, maintained for some time that CS_2 was not primarily a cause of nervous derangement but an "agent provocateur" of hysteria in those predisposed to it. However, the work of Koester disposed of that theory. He found, in experimental animals, degenerative changes in the cerebral cells and in the cells of spinal ganglia after CS_2 exposure. An autopsy performed on a worker who had had acute CS_2 delirium revealed severe diffuse changes in the cerebral cortex and the ganglion cells.

The first two papers on CS_2 poisoning in United States rubber workers were published in 1892 and attracted little attention. These give histories of three rubber vulcanizers, all men, who were sent to the State Hospital for the Insane, suffering from acute mania which subsided after a few weeks. In 1902 a third United States article appeared, describing a case of amblyopia in a woman who spliced inner tubes with CS_2 (Heath, 1902).

By 1914, United States plants in the rubber industry were using CS_2. Histories of intoxication from foremen reported irritability, depression, apathy, sudden outbursts of rage, or fear, with hallucinations, even maniacal seizures. Yet no physician in rubber centers knew of such occurrences nor that CS_2 was a poison to which rubber workers were exposed. In spite of the wealth of foreign literature on CS_2 poisoning in rubber workers, almost no notice was taken of the striking, if rare, cases occurring in American plants.

A few years later reports of CS_2 poisoning in viscose workers came from Europe, especially from Italy, where exposure was apparently excessive and mechanization little developed. Ranilletti, reviewing the histories of 100 cases of CS_2 poisoning (77 arising in the artificial silk industry, the rest in the extraction of fats and in the vulcanization of rubber), found that 80 of the patients showed involvement of the nervous system, and 52 of these were psychoses. In 20, gastrointestinal symptoms and anemia predominated. The psychoses were mainly of a maniacal type, with psychomotor excitement, delirium, hallucinations, distraught condition, or so-called dementia. The early stage, appearing after some months or even years of exposure is usually one of depression, but there may be a sudden attack of excitement with hallucinations. Ten of these workers had various forms of neuritis, the sensory nerves being less seriously affected than the motor. The peroneal muscles of the legs may be affected, and the gait is labored and dragging. Amblyopia was noted, and in one case a retrobulbar neuritis. Recovery takes place, according to Ranelletti, with surprising rapidity, as a rule, when the victim is removed from the exposure, even if the intoxication has resulted in "insanity."

During the Second World War, the blackout interfered with ventilation, and workers suffered from malnutrition. Vigliani studied 100 cases of chronic intoxication under wartime stress. He found that 160 to 800 ppm of CS_2 in work room air led to signs of poisoning in a few months. Palach (1948) reported 148 cases in two epidemics of CS_2 poisoning from Poland under the conditions of

enemy occupation. Both authors emphasized the prevalence of polyneuritis, affecting especially the legs, never the arms alone. Biopsy showed myopathy, with both hypertrophy and atrophy of fibers. Mild cases usually recover in two to three months, severe cases in six to eight months. If recovery is not noted in that time, it probably will not take place. An earlier belief that carbon disulfide polyneuritis is a temporary affliction with a favorable prognosis is not true in all cases.

Jump and Cruice (1904) were the first to call American attention to the viscose rayon industry as a source of CS_2 poisoning. They reported three cases in churn-room men in a report that attracted little attention. Alice Hamilton (1925) saw two cases of CS_2 poisoning in the United States. The first man had just returned to work in the viscose plant after a week on sick leave. He was very nervous, excitable, irritated by questions, and unable to bear any opposition. He had no wish to exaggerate his disability; on the contrary, he wanted to get back to his job in the churn room, provided he could sit down, for he had distinct loss of power in his legs. There was a certain degree of ataxia evident. The second man was in the hospital, with symptoms of acute psychosis. He seemed on the point of bursting into tears and suffered keen mortification over his loss of self-control, saying, "I was all right, doctor, till you came and stirred me up again."

In spite of the great growth of viscose manufacture in the United States in the 1930s, this danger to the employees was very tardily recognized; indeed as late as 1946 psychiatrists in state institutions for the mentally ill were entering in their records items such as "etiology occupational" or "unknown" or "exogeneous poison" but making no mention of CS_2, which apparently was not accepted as a cause of mental disease. Lewey (1941) examined 120 men who were employed at the time as churn-room men and spinners. This is the most thorough study made of early CS_2 poisoning in the United States. Mild forms of poisoning were found in 60 percent of spinners, whose exposure is not high, while in churners, whose exposure is much higher, severe poisoning was found in 20 percent in one plant, in 44 percent in the other. Lewey found that chronic carbon disulfide intoxication may involve all parts of the central and peripheral nervous systems, beginning with psychic symptoms, later peripheral neuropathy and damage to the cranial nerves, decrease of corneal and pupillary reflexes as well as pyramidal and extrapyramidal signs. A variety of clinical pictures very like Parkinson's disease were also observed.

SUMMARY OF CLINICAL SYNDROMES

Although the chronic form of poisoning is far more serious, we do see the acute cases in which the concentrated vapors cause irritation to the eyes, nose, and skin. In chronic carbon disulfide poisoning the nervous system bears the brunt of damage. Neuritis affecting peripheral or cranial nerves (optic and auditory) is very common. Usually the trouble begins with a sensation of crawling over the skin, formication, a tendency for the arms and legs to "go to sleep," a sensation of coldness and heaviness, and a curious feeling that the hand and foot belong to someone else. Pain is associated with these symptoms and tenderness along the nerve trunk, and at the same time tests may show touch, pain, and the temperature sense to be heightened, rarely diminished. There is usually constant or paroxysmal pain in the distribution of one or several nerves and, during the night, pain in the legs may reach an intolerable intensity. Any of the nerves may be affected, but those more usually involved are the radial and ulnar, the sciatic and external peroneal. These symptoms are followed soon by signs of motor nerve involvement. The worker complains of fatigue, increased loss of strength and weakness in the legs. The reflexes are most often diminished.

The course of carbon disulfide neuritis is slow—slower than that of alcoholic, rheumatic, or syphilitic origin. Recovery proceeds with extreme slowness, and the prognosis must be guarded, because the atrophy, pain, paresthesia, and other manifestations may persist even if the victim quits his job.

The most striking and the most disastrous effects of carbon disulfide poisoning are upon the brain. The mental symptoms run the gamut from simple irritability and depression to manic-depressive insanity. If the basal ganglia are involved, Parkinsonian palsy occurs. In typical cases the attack of active or violent mental disturbance comes on fairly suddenly, but careful questioning of the family and working mates always will bring to light an earlier stage of emotional upset, irritability, depression, and complaint of loss of memory. Even in milder poisoning, changes in personality are evident, especially in the man's relations with his wife and children, and the victims realize this but are powerless to help it. Sleeplessness, dreams, and loss of memory are frequent complaints. Disturbances of vision, though rarely of a pronounced character, are present often and give valuable aid in the diagnosis. Central scotoma for color, abnormal color vision, loss of visual acuity, and paralysis of accommodation have been described (Gordy and Trumper, 1943).

Gastric disturbances are common in some reports with symp-

toms that mimic those of a peptic ulcer. Heart, liver, and kidney damage are described by some authors as associated with high and continuous CS_2 exposure. Beginning in 1950, chronic poisonings have been reported which presented symptoms very similar to those found in pre-senile cerebral arteriosclerosis. Workers in the age group from forty-two to fifty-five are usually affected, and they often have associated kidney damage. While some cases present only one aspect of the atherosclerotic process, some present a complete picture of cerebral, renal and myocardial sclerosis (Browning, 1965, p. 705). Von Rechenberg in 1957, and Vigliani and Cazzullo reported that workers exposed to CS_2 first noted pain in the calf of the leg with difficulty in walking (Browning, 1965, pp. 710–711). In some cases electrocardiograms suggested previous myocardial infarctions (Brieger, 1961). At autopsy atheromatous plaques are found, general arteriosclerosis with retinal vessel changes resembling those in hypertension and glomerulosclerosis.

While some of these reports are old and describe European experience in rubber factories—because CS_2 is used as a raw material in the manufacture of viscose rayon and has excellent solvent properties—exposures continue. According to Kleinfield and Tabershaw (1955) poisoning is rare in the United States. Brieger (1961) reviewed the knowledge of CS_2 toxicity derived from laboratory animal studies as well as occupational illness. The biological behavior of CS_2 has the attention of a number of research laboratories, especially in Italy and Czechoslovakia, summarized in a conference held in Prague in 1966 (Brieger and Teisinger, 1967). The details of the biologic effect of absorbed CS_2 are to be found in Brieger's review (1961) and Browning's text (1965), pp. 702–712). Briefly stated, CS_2 has been shown to have a toxic action on protein metabolism. In addition, by hepatic damage, CS_2 causes nervous system disease and hypercholesteremia which leads to early arteriosclerosis.

At present the accepted threshold limit value (TLV) in the United States is 20 ppm (*Documentation of the Threshold Limit Values*, 1971). Russia in 1967 felt that a 4 ppm limit afforded more safety, and the Czechoslovakian observers in 1969 felt a 10 ppm would be safer than our TLV.

Direct measurement of blood and urine for carbon disulfide levels gives some evidence of intensity of exposure (Patty, 1963). A more specific chemical test is available to evaluate exposure by measuring urine metabolites of CS_2 using the iodine-azide test developed by Djurič, Surdučki, Berkes (1965).

SECTION FIVE

ORGANIC HIGH POLYMERS

The organic high polymers, regardless of their ultimate applications, are similar to the extent that they are based upon the structural repetition of smaller units (monomers) and often contain additional substances which are not actually part of the polymer itself. Toxic phenomena associated with the high polymers may be related to their unreacted or under-reacted constituents, to various auxiliary substances, or to degradation products. It is uncommon for a fully reacted or "cured" polymer to cause illness, and most of these materials show a high degree of biological inertness and insolubility. The term elastomers is applied to those polymers which can be stretched easily and which return to their original dimensions when the stressing force is removed. Natural and synthetic rubbers are elastomers. Linear macromolecules with high longitudinal mechanical strength and lateral flexibility can be utilized to form synthetic fibers for textile applications.

The term resin has an imprecise meaning in the plastics industry and may be used interchangeably for the term plastic. In some applications resins are short-chain uncured polymers which are subjected to further polymerization and hardening. In other applications resins are granular fully-cured thermoplastics which can be heated for extrusion, molding, or calendering.

The principal plastics may be divided into two groups: (1) thermosets, which cannot be reformed or melted after the initial "cure;" and (2) thermoplastics, which can be heated and reshaped repeatedly. A simple classification may be outlined in the following manner.

Table 8
Principal Plastics

Thermosets	
Aminos (urea and melamine)	Polyesters (and alkyds)
Epoxys (ethoxylin)	Polyurethanes
Phenolics	Silicones
Thermoplastics	
Acetals	Nylons
Acrylics	Polycarbonates
Acrylonitrile-butadiene-styrene	Polyethylene
Cellulosics (cellulose acetate, propionate, butyrate)	Phenylene oxide
Fluoroplastics	Polypropylene
Polyvinyl alcohol	Polystyrene
Polyvinyl chloride	Polyvinylindene chloride
	Polysylenes

AMINOS

The amino resins are almost entirely based upon urea-formaldehyde and melamine-formaldehyde and are typically used for electrical switch housings, knobs, molded dinnerware, adhesives, plywood glues, coatings, and industrial laminates. Crease-resistant garments are produced by pressing to the desired shape textiles impregnated with suitable amino resin formulations. Hexamethylenetetramine, called "hexa," is used as a stabilizer in amino resin systems to prevent premature hardening.

harmful effects

The component of primary toxicological interest is formaldehyde, which is present in the production of the resin or in association with incompletely cured products. At concentrations above 3 ppm formaldehyde is irritating to the eyes and upper airway. Higher levels cause severe burning sensations, coughing, and profuse lacrimation. Deep lung irritation in man has not been

observed, but it presumably could occur under extreme circumstances. Skin sensitization to formaldehyde in the vapor state is unusual, and pulmonary reaction has not been reported. Persons who are already sensitized, however, may show a skin reaction to this type of exposure. Cross reactions to other aldehydes have been noted in sensitive individuals. Formaldehyde is a potent skin irritant and sensitizer; eczematous reactions are observed in workers handling improperly cured crease-resistant textiles (Fisher et al., 1962). Hexamethylenetetramine decomposes to form formaldehyde and is a possible source of irritating and sensitizing cutaneous reactions, but it has never been a major problem either in this application or in the explosives industry. Acetic acid accelerators do not present unusual problems.

EPOXY RESINS

Cured epoxy resins have outstanding resistance to heat and chemicals and find wide application in reinforced plastics, coatings, adhesives, and in casting, "potting," and encapsulation. The typical resin is prepared from epichlorohydrin and a polyhydroxy compound (e.g., bisphenol A) in the presence of a curing agent. Epoxy resins are cured by cross-linking agents known as "hardeners," such as the polyamines (diethylenetriamine, triethylenetetramine, piperazine) or the acid anhydrides and polybasic acids (phthalic anhydride, adipic acid). Catalysts perform a similar curing action but do not themselves act as cross-linking agents. Common catalysts include various polyamides, monoethylamine, and tertiary amines such as triethylamine and benzyldimethylamine. Diluents—phenyl, allyl, and butyl glycidyl ether, styrene oxide, styrene, and other epoxides—may be utilized to reduce the viscosity of uncured resin systems.

biological action

Epichlorohydrin, bisphenol A, and liquid epoxy resins are skin irritants and sensitizers. Epichlorohydrin is highly irritating and can produce severe burns, but there have been no examples in man of serious pulmonary or systemic injury. Because this compound can cause renal damage in experimental animals, however, persons handling epichlorohydrin in the manufacture of epoxy resins should be under surveillance (Gage, 1959). The reactive diluent glycidyl ethers and related epoxy compounds are cutaneous irritants and sensitizers. It has been pointed out that the epoxy group may be associated with radiomimetic effects, presumably reflecting biological alkylation (Kotin and Falk, 1963). There is no evidence, however, that these materials are comparable to the nitrogen mustards in this regard, or that there is an industrial hazard related to this property.

Industrial health problems most frequently arise from exposure to aliphatic polyamine hardeners, which can cause severe primary irritative and hypersensitivity dermatitis and asthma-like reactions. These amines are strongly basic (pH 13–14) and can produce chemical burns of the skin. Some contain dye bases that may yellow the skin upon oxidation. Cutaneous amine reactions cause erythema, intolerable itching, and severe facial swelling. Blistering with weeping of serous fluid, crusting, and scaling may occur. An apparently permanent hypersensitive state may develop with extreme reactivity to amines. Examples are recorded of persons with previous amine dermatitis who experience a dramatic return of symptoms upon minute re-exposure. Highly sensitive persons may also react to cured resins containing small amounts of unreacted amine hardeners.

Although pulmonary reactions in the modern plastics industry are most commonly attributed to components of polyurethane systems, amine hardeners for epoxies do cause bronchospasm and coughing episodes which may persist for several days after the cessation of exposure. Repeated attacks of acute amine-induced respiratory disease are often associated with increased responsiveness to these compounds, for faint traces of amine vapors in the air have been sufficient to trigger intense return of symptoms in persons with a history of amine asthma. Acid anhydride and polyamide hardeners and catalysts are contact irritants, but industrial problems related to their use have been uncommon.

Diluents such as xylene or the ketones do not sensitize but defat the skin with repeated contact. Glass fibers used in many applications are mechanically irritating and pruritic and may be released when inert laminates or other forms are cut or tooled. Sawing, machining, and other manipulations of solid cured resins which produce heat may give rise to degradation products that contain free amines or unreacted epichlorohydrin.

control

Prevention of problems from epoxy exposure is based upon meticulous cleanliness of work areas. Mixing of resin and hardener and the application of the liquid formulation should be done under appropriate ventilation. Material which is spilled on the skin should be removed promptly with soap and water. Organic solvents used for this purpose tend to spread contamination and irritate the skin.

PHENOLICS

The modern plastics industry is based upon Leo Baekeland's discovery (1909) of phenol-formaldehyde thermo-setting materials. The term phenolic resins now encompasses a variety of similar

products made by reacting a phenol-like compound with an aldehyde. Commercial "phenols" include phenol, cresol, xylenol, p-t-butylphenol, and resorcinol. Important aldehydes include formaldehyde, paraformaldehyde, and furfural. Catalysts include hexamethylenetetramine (referred to as "hexa"), ammonia, and various other amines. The applications of the phenolic resins are similar to those indicated for the amino resins, which have similar structures and properties. Large quantities of phenol-formaldehyde resins are used in bonded brake linings and clutch facings and as bonding agents for foundry sand molds.

worker illness

Important industrial effects are those of dermatitis. Phenol is a potent primary irritant, and resorcinol, furfural, and formaldehyde are irritants and sensitizers. Furfural is a photosensitizer. In some applications cashew nut shell oil has been used as a phenolic component in the resin formulation. This oil is chemically related to poison ivy resins, but the oil used in industry is said to have been treated to render it safe for handling. Nevertheless persons highly sensitive to Rhus-type oleoresins may be reactive.

POLYESTERS AND ALKYDS

Materials of the polyesters and alkyds group are fundamental to reinforced plastics technology, which is increasingly important in the boat and automotive body industry and in the market for structural panels, electrical appliances, and home furnishings. The reinforcement is generally provided by glass fiber textiles, and the typical structure is composed of laminations of polyester and a textile. The polyesters themselves are derived from the reaction of a polyfunctional acid (e.g., phthalic or maleic add anhydride) with a polyfunctional alcohol (e.g., propylene glycol, ethylene glycols, pentaerythritol). Polyesters are dissolved in styrene and stabilized with an inhibitor such as hydroquinone to form a viscous syrup-like liquid which does not readily solidify. When gelation is desired, a catalyst, usually a peroxide (e.g., benzoyl peroxide or methyl ethyl ketone peroxide), is added. To accelerate this styrene cross-linking solidification, promoters or accelerators (dimethylaniline or cobalt salts) may also be added. While styrene is generally the reactive solvent and cross-linking group between the polyester macromolecules, other equivalent compounds may be used for special purposes. Methylmethacrylate increases resistance to weathering, diallyl phthalate resists polymerization of the uncatalyzed syrup, and triallyl cyanurate increases resistance to elevated temperatures.

toxic effects

The acid anhydrides, when applied to the damp skin, can cause burns. The dusts are irritating to the eyes and upper airways.

There is no important systemic toxicity, however. Styrene (vinyl benzene) vapors are irritating and narcotic at high concentrations and can produce a "styrene sickness" consisting of nausea, headache, fatigue, dizziness, and drowsiness. The compound is not a hematopoietic poison. The irritant properties are sufficiently potent to protect workers against serious effects. Organic peroxides are highly irritating to epithelial tissues and are flammable oxidizing agents. There is evidence that benzoyl and methyl ethyl ketone peroxides are skin sensitizers as well. Dimethylaniline and cobalt naphthenate are both sensitizers; the former can produce most of the effects of aniline. Although the allyl group has well-known toxic properties, serious occupational hazards have not been associated with diallyl phthalate and triallyl cyanurate, both of which are irritating. Industrial health problems from the polyester group are infrequent, and most of them may be attributed to the mechanical effects of glass fibers upon the skin.

POLYURETHANES

Urethane polymers are formed by reactions between a polyol (polyhydroxy) compound and a diisocyanate. Polyurethanes are used in coatings, elastomers, and foamed cushioning or flotation applications. Catalysts used to promote the reaction include organotin compounds, cobalt naphthenate, or various amines. In the course of polymerization reactions, carbon dioxide is evolved giving rise to bubbles or a foam. To obtain additional gas, a foaming or blowing agent may be included to supplement gases evolved in the basic reaction. Polyurethane foams are typically poured or sprayed into position, where the so-called final cure occurs.

reports of occupational disease

Although amines are irritating and sensitizing, the main health problem associated with polyurethane plastics arises from the diisocyanates, most commonly toluene diisocyanate referred to as TDI. Vapors of these compounds invariably become airborne in polymerization reactions, especially since heat and gas are evolved. Clinical experience with TDI shows that it is a potent irritant of the eyes and upper airway. With prolonged exposure there may be significant respiratory distress with dry painful cough, chest pain, and occasional blood-streaking of scant sputum. In some cases fever, cyanosis, and general feelings of distress are noted. The x-ray in these situations has been usually normal, although diagnoses or descriptions of bronchitis, "increased markings," or "reticulation" have been made (Brugsch and Wilkins, 1963). With continued or repeated exposures to TDI the clinical picture has been dominated by evidence of bronchospasm, sometimes very severe, with chest tightness, wheezing,

cyanosis, and collapse. Some workers become exceedingly sensitive to TDI vapors and respond dramatically to minute amounts of this material in the air. The nature of the "sensitivity" to TDI has not been clearly established. There is experimental evidence for antigen-antibody mechanisms, while other observations suggest that a direct irritant effect on susceptible tissues is responsible. It is also not clear whether chronic injury occurs, either in response to repeated acute episodes or to low-level long-term exposures without prominent symptoms.

control and therapy

There is evidence that the already low threshold level value (TLV) of 0.02 ppm is not sufficiently low to preclude the development of bronchospastic responses in "sensitized" persons. Peters and his associates (1970) have shown that TDI concentrations in the order of one-tenth of the TLV may cause significant depressions in the forced vital capacity and forced expiratory volume in one second.

Treatment of these pulmonary responses is based almost entirely upon control of exposure. For highly sensitive people, work with polyurethane foams must be eliminated. Engineering measures are essential to the adequate control of vapors. Bronchospasm responds to bronchodilators; oxygen may be indicated in severe cases.

SILICONES

Silicones are composed of chains of alternate atoms of oxygen and silicon. Various organic groups can be attached to the silicon atoms, and the amount of cross-linkage between chains by these groups determines whether the polymer will be hard, an elastomer, or a fluid. The fully reacted polymers are remarkably inert and thus find use in heart valves, prostheses, heart-lung machines, and artificial kidneys. Major industrial uses are in lubricants, encapsulations, dielectric laminates, and "non-stick" release compounds.

The biological properties of the silicone intermediates have not been studied. Of the silicones, chlorosilanes are corrosive to mucous membranes; ethoxysilanes, less so. No reports of injury have appeared in the clinical literature. Various metallic soaps, acetic acid, and toluene solvents may be used in final applications.

ACETAL RESINS (POLYFORMALDEHYDE)

Of the acetal resins, polyformaldehyde is a material of unusually good mechanical properties. It may be thermally degraded, as in an overheated molding machine, to formaldehyde with its well-recognized irritant and sensitizing properties.

ACRYLICS

Acrylic plastics such as Lucite and Plexiglas are based upon methyl and ethyl acrylate and methacrylate; methyl methacrylate is the major constituent. These are respiratory and cutaneous irritants, the acrylates more so than the methacrylates, but have no known cumulative or chronic toxic properties. Methyl methacrylate vapors can produce headache, irritability, and other nonspecific symptoms. Acrylic paints are based upon a water emulsion of acrylic polymers, which are of no known biological importance.

ACRYLONITRILE-BUTADIENE-STYRENE

toxicity

The materials of this mixture can be varied in relative quantity and treatment to produce a family of plastics suited to home appliances, automobile instrument panels, boats, recreational vehicle bodies, and a heterogeneous group of other applications.

The monomeric reactants all have biological properties absent in the finished product. Butadiene is a weak irritant and narcotic gas, which is combustible and explosive. It is used primarily in the production of synthetic rubber. Acrylonitrile is a flammable volatile liquid which can be absorbed through the skin, lungs, and intestinal mucosa. Its biological properties are those of cyanide, and the intensity of intoxication appears to correlate with the blood level of cyanide ion. That the toxicity of acrylonitrile is related to other pharmacological properties has not been established. Medical therapy for acrylonitrile poisoning is the same as that for hydrogen cyanide poisoning and is based upon the formation of cyanmethemoglobin. Since acrylonitrile can pass through the intact skin, special attention to decontamination and the clean-up of spills is especially important. The compound can also penetrate various types of rubber, and gloves may not provide suitable protection.

CELLULOSE DERIVATIVES (CELLULOSICS)

Cellulose acetate, propionate, and butyrate have almost entirely replaced cellulose nitrate, which is highly flammable and is a source, when burned, of nitrogen dioxide gas. Modern cellulosics are used in nontoxic films and coatings in small parts such as knobs, eyeglass frames, and pencil barrels. Toxicity is not associated with these polymers. The synthetic process may involve exposure to solvents and organic acid compounds which may result in skin reactions.

FLUOROPLASTICS

Fluoroplastics vary somewhat in composition and include polytetrafluoroethylene, fluorinated ethylenepropylene, and polyvinylidene fluoride. These materials are extremely inert biologically and can be used for human organ prostheses as well as for

highly resistant insulations, chemical piping, containers, gaskets, and coatings. The widely used Teflon is a fluoroplastic.

worker illness

Harmful worker exposures are not commonly related to the production of the polymers themselves, inasmuch as the reactions are conducted in closed systems. The chemical intermediates include fluorohydrocarbons of the so-called Freon type, which are relatively inert or have only narcotic properties at high concentrations. More active reactants may occur in the process and may be highly corrosive or possibly nephrotoxic. Such exposure would be most unlikely. Illness, which has been related to the fluorohydrocarbons, is described by the term "polymer-fume fever," a syndrome similar in character to influenza (Lewis and Kerby, 1965). Symptoms appear within some four to five hours of exposure to sublimates or thermal decomposition products of fluoroplastics. In most situations the toxic material is generated when polymer dust contaminates tobacco products. The temperature of burning tobacco or equivalent heat sources is sufficient to cause physical and pyrolytic changes in the otherwise inert polymer. Chest tightness and dyspnea are early and common complaints. General malaise, headache, and cough are noted, and chills with fever to 104°F follow the onset of symptoms by some twelve hours. The acute illness may be alarming and uncomfortable when it is severe, but it is short in duration and without known sequelae.

The composition of the thermal decomposition products is not well defined, and it is doubtful that there is a single compound responsible for polymer fume fever. Under some circumstances, transient pulmonary edema has been observed. This is not surprising since hydrogen fluoride and other highly irritative materials are contained in fluoroplastic pyrolysis fume. There is no evidence, however, of deaths or chronic illness in man from this cause.

Control of whatever problem exists is effected through warning to the worker, prohibition of tobacco in the work place, hand washing, and attention to airborne dust and to heat sources.

NYLONS, POLYAMIDES

Nylons are polyamides used in fibers, filaments, castings, and extrusions and can be classified into two families: the diamine-dibasic acid type and the condensed amino acid type. The finished plastic in either case has no known toxic effects. Diamine-dibasic acid nylons are prepared by reacting a diamine such as hexamethylenediamine with an acid such as adipic or sebacic acid. The diamine has a primary irritant and sensitizing effect on the skin and is irritating to the eyes and upper airway. The dibasic acids are not a source of illness. Amino acid nylons are formed from the

condensation of materials such as E-caprolactam, which is of little biological interest. Rare skin reactions to virgin nylon products have been described and have been generally attributed to residual reactants or to low-molecular weight polyamides (Morris, 1960). Dyes and finishes applied to nylon for wearing apparel have also been uncommon causes of contact dermatitis.

The most prominent air contaminant in many typical polycaprolactam nylon operations is derived from an eutectic mixture of diphenyl and diphenyl oxide. This material is heated and pumped under pressure as a heat transfer fluid. Small leaks give rise to vapors and mists of which the workers complain, with nausea, but of no described systemic toxicity. In heat transfer applications the material may be heated to temperatures as high as 700°F. There is an obvious potential for severe burns. Heat transfer agents of this type have been used in organically cooled and moderated nuclear reactors. High temperature and radiation fields modify diphenyl and diphenyl oxide to a variety of high-boiling residues which must be removed from the coolant streams. Thorough toxicological studies have not been performed upon these thermal and radiation-induced degradation products, but carcinogenic and toxic molecules may be present.

POLYCARBONATES

Polycarbonates are polyesters formed by the polymerization of dihydric phenols through carbonate linkages. The plastic is used primarily for small mechanical parts such as gears and cams. Biological properties have not been associated with the finished polymer. However various synthetic approaches to the polycarbonates utilized potentially harmful compounds such as bisphenol A, phosgene, dioxane, and other solvents.

POLYETHYLENE, POLYPROPYLENE, POLYOLEFINS

Materials of this group are widely used in packaging, housewares, toys, and vapor barriers. The polymerizations take place in closed reaction vessels under the influence of catalysts such as benzoyl peroxide, metallic oxides, or active organometallic compounds such as triethyl aluminum. The finished resin, sold commercially for thermoplastic molding, extrusion, or other applications is essentially without biological properties. Under conditions of thermal stress above 250°C these polyolefins undergo degradation to compounds which are irritating and injurious. The hazard is not greatly different from that associated with any combustion of organic materials.

POLYSTYRENE

Polystyrene is prepared from the polymerization of styrene (vinyl benzene) under the influence of organic peroxides such as benzoyl peroxide, lauroyl peroxide, etc. Styrene can polymerize

prematurely in storage; this tendency is controlled by the addition of inhibitors, usually phenols such as butylcatechol or hydroquinone, both sensitizers. Polystyrene is used in appliances, toys, furniture, and a variety of packagings.

Monomeric styrene is strongly irritating to the eyes, pharynx, and upper respiratory tract and can produce headache, nausea, vomiting, and primary skin irritation. No chronic toxicity has been associated with styrene exposure.

VINYL POLYMERS AND COPOLYMERS

The vinyl group of plastics includes polyvinyl chloride used in floor tiles, ducting, waterproof clothing and upholstery, insulations, and pipe; polyvinyl acetate used in adhesives and coatings; polyvinyl alcohol (water-soluble); and polyvinylidene chloride. In all of these applications the finished plastic has been found to be without injurious properties.

Until recently the monomeric precursors have not been thought to have toxicological importance, although it has been known that vinyl chloride and vinyl acetate may produce dizziness and confusion. It has become apparent, however, that vinyl chloride may be a potent carcinogen inasmuch as six cases of hepatic angiosarcoma have been reported among the employee population of a single plant in which vinyl chloride is polymerized. That this striking clinical phenomenon has occurred in other industrial establishments or that it is definitely caused by vinyl chloride remains to be established. The incidence of hepatic angiosarcoma in the entire population of the United States approximates 25 cases per annum.

There are no reports of occupational illness associated with exposure to vinylidene chloride (1,1-dichloroethylene), although the toxicological properties of the compound are similar to those of carbon tetrachloride.

Thermal degradation products include the monomers and hydrochloric acid fumes.

toxic effect

In the last several years a distinctive industrial disease, occupational acroosteolysis, has been observed in men working as "polycleaners" in several PVC production facilities (Wilson et al., 1967). The disease is currently thought to affect only those people who manually clean PVC reaction kettles in which polymerization occurs. The disease does not occur in those who handle the finished thermoplastic resin. The actual toxic agent and the means whereby it causes illness are not presently known. The clinical picture is that of Raynaud's phenomenon with discomfort and blanching of the hands on exposure to cold. Unique roentgenological changes are noted in the distal phalanges of the hands and may

be present in asymptomatic individuals. The changes consist of loss of cortex of one or more tufts or complete lytic destruction of the tuft and a portion of the adjacent shaft. Healing occurs with a fragmentation of the affected area and union of the fragments. The fingers themselves appear upon inspection to be shortened and "clubbed." Since it is possible to clean reaction vessels by techniques which do not require hand scraping, new cases of this disease should not occur unless longer experience demonstrates that the toxic agent is present in other operations.

Monomeric vinyl chloride is produced by several processes, one of which is based upon the addition of hydrogen chloride to acetylene in the presence of mercuric chloride. This process has been responsible for the introduction of mercury compounds into natural bodies of water, from which mercury is eventually absorbed by fish, including those species used by man as food.

ACRYLAMIDE

worker disease

Acrylamide is a vinyl monomer used in the production of special polymers. These have applications as flocculating aids for the precipitation of suspended solids from aqueous systems and as special chemical grouts. Although the polymer is nontoxic, the absorption of acrylamide through the skin or from dusts has been associated with serious neurological consequences (Garland and Patterson, 1967). A variable polyneuropathy with motor and sensory impairment is marked by numbness, paresthesias, and weakness. Ataxia, tremor, dysarthria, and other central nervous system signs are consistent with mid-brain lesions. Although recovery over the course of months has been the rule in mild cases, permanent neurological sequelae are observed in severe intoxications.

POLYVINYL-PYRROLIDONE

occupational experience

Bergmann et al. (1958) introduced the concept of pulmonary damage following exposures to hair sprays and named the disease thesaurosis. McLaughlin and his colleagues (1963) reviewed the literature to 1963 and reported on a total of 755 chest x-rays of British hairdressers. Cares (1965) presented the United States experience. The reported cases present as sarcoid-like disease clinically, by chest-x-ray, and by histopathologic findings. Alternative diagnoses in the literature are interstitial fibrosis and foreign body granulomas. With the present data thesaurosis appears to be chiefly a problem in differential diagnosis. The cases seen by one of the authors (HLH) have proved to be Boeck's sarcoid with lesions in organs in addition to the lung, or chronic beryllium disease.

McLaughlin et al. conclude that it is possible to diagnose thesaurosis by chest x-ray perhaps because of hair spray particles in the lung. They could not correlate quantity of spray inhaled and clinical findings. Their single case in a hairdresser was thought to

be an example of unusual hypersensitivity. Gowdy and Wagstoff (1972) describe five cases with pulmonary chest x-ray infiltrates and four with respiratory complaints, all exposed to a variety of aerosols and all cured by freedom from exposure. Four biopsies and lung function tests were nonspecific. Further, these authors surveyed 227 beauty operators and found none ill but 11 with increased bronchovascular markings on chest x-ray.

The material used exclusively in the United States is polyvinylpyrrolidone (PVP), rather than shellac which is used in England. PVP, used as a plasma expander, has proved safe. Oils and propellants used in hair sprays may have a detrimental effect. However, the evidence at present, in view of the large amount used by young women, is that hair sprays are harmless.

ADDITIVES

The primary polymers previously outlined are modified through the addition of materials which are selected to impart particular, desirable properties to the finished product. These additives, not being large and thus inert polymeric macromolecules, may have biological characteristics which far outweigh those of the basic plastic under consideration.

plasticizers

Plasticizers are mixed into polymers to increase flexibility and workability. Phthalate esters account for some two-thirds of total domestic plasticizer production and include di(2-ethylhexyl) phthalate, diisooctyl phthalate, and dibutyl phthalate. Adipate, sebacate, and azelate esters are also commonly used, especially when low-temperature flexibility is desired. These esters have a very low order of toxicity. Polyester and epoxidized plasticizers are also of little industrial health importance, although the epoxy materials can be sensitizers.

Phosphate esters, among the first plasticizers to be developed, impart flame resistance to polymers. Tricresyl phosphates have been the most important. It is believed that tricresyl phosphate used as a plasticizer is generally free of ortho isomer, which has prominent neurotoxic properties. Triphenyl phosphate, cresyl diphenyl phosphate, and octyl diphenyl phosphate are also used. The question of the purity of materials in this group and freedom from neurotoxic components is often difficult to establish in an industrial setting. The low vapor pressure of the aromatic phosphate esters is a source of protection.

Other plasticizers include chlorinated paraffins and chlorinated biphenyls. The latter group is associated with chloracne and hepatic injury; the paraffins lack this toxicity.

Flame retardant properties can be inherent in certain plastics

because of high chlorine content or, as in the case of the polycarbonates, because they evolve carbon dioxide upon thermal decomposition. Flame retardant additives of hygienic interest include tricresyl phosphate, chlorinated di- and triphenyls, bromine compounds, halogenated phosphates, and antimony trioxide. Flame retardant intermediates which actually become incorporated into the polymer generally contain chlorine or bromine.

Stablizers retard the natural degradation of plastics due to light and heat. Potentially hazardous stabilizers are lead salts or soaps, barium and cadmium systems, and organotin compounds. Ultraviolet absorbers are added to protect polymers against wavelengths which tend to disrupt bonds in organic material. Typical absorbers are found among the benzophenones, benzotriazoles, aryl esters of salicylic, benzoic, and terephthalic acids, and organonickel compounds. Antioxidants include alkylated phenols and bisphenols, amines, and organic phosphites.

biological properties

For the most part, the biological properties of these additives are not well established. The metallic compounds and organometallics do, however, present a known hazard. Exposure to these additives tends to be small because they are introduced primarily in early steps of the formulation, and few workers are exposed.

organic peroxides

Organic peroxides are used to cure polyester resins, to initiate polymerization of vinyl and diene monomers, and to cross-link polymer chains, as in polyolefins or silicones. More than forty-five organic perioxide compounds are available commercially. Although not all peroxides are hazardous, they are, in general, strong oxidizing agents capable of causing skin irritation or burns and severe eye damage. Peroxides on the skin or in the eyes should be removed promptly with large amounts of water. The use of face shields and protective clothing is indicated for those who handle organic peroxides. These compounds tend to be unstable and to undergo spontaneous decomposition. Fires or explosions can result from the contaimination or the improper storage of organic peroxides.

inert fillers and fibrous reinforcements

Inert fillers and fibrous reinforcements are added to many formulations to improve their mechanical properties, to act as extenders to reduce costs, or to impart certain special properties. The addition of silica, asbestos, talc, mica, glass flakes and fibers, and other materials is common. Some of these substances have inherent biological properties which may create a hazardous environmental situation at the time of polymer formulation or when

the finished plastic is cut or machined. Under these circumstances potentially injurious dusts may be generated. Rapid developments within the plastics industry have created high thermal conductivity polymers (beryllia-filled epoxy), antifriction elastomers (molybdenum disulfide-filled), radiation shields (lead-filled polyolefin), and plastics reinforced with exotic fibers (boron, sapphire). Biological effects may be associated with the use of some of these materials.

foaming agents

Foaming agents may be added to increase the porosity of plastics which normally foam or to create foamed structures from plastics which have no inherent foaming properties. Foaming agents may generate gas by either physical or chemical means. Physical foaming agents are generally volatile liquids which become gaseous and create cells under the influence of exothermic reaction or externally applied heat. Aliphatic hydrocarbons of the petroleum ether, ligroin, or light spirits type are flammable but do not have prominent toxic properties. Halogenated aliphatic hydrocarbons such as methyl chloride, methylene chloride, and trichloroethylene are also used as foaming agents. The aliphatic fluorocarbons are essentially inert. So-called chemical blowing agents which are foaming agents are compounds which decompose under the influence of heat to yield a gas, usually nitrogen. The most common commercial chemical foaming agent is azobisformamide, which is considered nontoxic. Azobisisobutyronitrile, however, is toxic, and releases nitrogen gas and a residue of tetramethyl succinic dinitrile, which persists in the foam. This compound is a convulsant in animals and has been believed to be the cause of headache, nausea, and other ill-defined systemic complaints in workers. The substitution of other blowing agents has corrected the problem. Azobisisobutyronitrile may be used in small amounts for the catalytic polymerization of vinyl plastics. Dinitrosoterephthalamide, also used, has not been a source of industrial illness.

ELASTOMERS • 2

Elastomeric polymers are frequently constructed of many of the same monomers used in plastics. Proportions, minor constituents, catalysts, and reaction conditions are varied to yield a product with elastic properties. From the medical point of view, an important distinction between some synthetic elastomers and other macromolecular polymers is that "cured" rubbers can occasionally be a source of toxic ingredients added in the formulation stage. Cured plastics are rarely associated with this type of problem. Elastomers of the silicone, polyurethane (referred to as spandex), and fluorinated groups do not present those problems of the more rubber-like elastomers.

Synthetic Elastomers
- Acrylonitrile-butadiene copolymers
- Chlorosulfonated polyethylene
- Ethylene-propylene polymers
- Fluorinated copolymers
- Polychloroprene, referred to as Neoprene
- Polyisobutylene
- Polysulfide rubber
- Polyurethane elastomers
- Silicone rubbers
- Styrene-butadiene copolymers

ACRYLONITRILE-BUTADIENE COPOLYMER

Elastomers of this group are highly resistant to solvents and oils and are used for hoses, gaskets, and protective clothing. Nitrile rubber is frequently plasticized with organic phosphates, phthalic esters, or dibenzyl ether. Dibenzyl ether is not believed to have prominent toxic properties. The biological properties of butadiene and acrylonitrile have been well established over many years of production of nitrile rubber. There have been few problems from industrial experience.

CHLOROSULFONATED POLYETHYLENES

Such elastomers are prepared by the reaction of sulfur dioxide and chlorine on polyethylene. They are used in white sidewall tires, hoses, tank linings, and elsewhere where resistance to heat and oxidation is required. These polymers are cured with oxides of lead or magnesium. Accelerators include mercaptobenzothiazole, benzothiazolyl disulfide, and dipentamethylenethiuram tetrasulfide. Compounds of this group are known skin sensitizers and may be present in finished rubbers in toxic amounts.

ETHYLENE-PROPYLENE COPOLYMERS AND TERPOLYMERS

To produce an elastomeric polymer, olefins are reacted under the influence of a coordination catalyst such as vanadium oxychloride or diethylaluminum chloride. Peroxides may be used in the cure, although the incorporation of a third monomer such as dicyclopentadiene will permit the use of conventional sulfur vulcanization. The toxicity of this alicyclic hydrocarbon is not established, but at present no biologic activity is known. Elastomers of this group are resistant to atmospheric and chemical attack and are used in hose, belts, gaskets, and footwear.

FLUORINATED ELASTOMERS

Copolymers of vinylidene fluoride and chlorotrifluoroethylene or perfluoropropylene are highly resistant elastomers used in gaskets, seals, and other specialized applications where high-cost materials can be afforded. The elastomers are biologically inert, although extreme heating can produce a hazardous exposure to harmful substances. Curing agents include diamines, peroxides, or ionizing radiation.

NEOPRENE

toxicity

Neoprene rubber is highly resistant to oil, solvents, oxygen, ozone, and heat. It is of greatest service in mechanical and automotive applications such as belts, hose, seals, and gaskets. Neoprene is formed from the polymerization of chloroprene, a colorless liquid which can be irritating to the skin and to the respiratory tract. Animal experiments show evidence of liver and kidney damage, thought to be nonspecific. The most unusual effect of chloroprene or perhaps of small polymeric intermediates is the temporary loss of hair which has been observed in neoprene producers. Termination of exposure is associated with the return of normal hair growth.

POLYISOBUTYLENE

Butyl rubber is formed from the polymerization of isobutene (isobutylene) with small amounts of chloroprene or butadiene. The reaction is carried out in a closed system with an aluminum chloride catalyst. Butyl rubber is highly impervious to gases and finds its major use in inner tubes, air chambers, and dielectrics. Isobutene is an anesthetic and asphyxiant gas, but it is only a hazard if concentrations are high enough to produce asphyxia. Under these circumstances a concurrent hazard of explosion exists.

POLYSULFIDE RUBBER

Elastomers of this group are highly resistant to oils, solvents, and weathering and are therefore found in caulking compound, coatings, adhesives, and mechanical components. Polysulfide elastomers are based on the condensation products of sodium polysulfides and dichloro compounds such as ethylene dichloride. More complex chlorinated hydrocarbons yield products with improved

properties. This group of elastomers is plasticized with biologically active compounds such as tetramethylthiuram disulfide or benzothiazolyl disulfide. Organic peroxides and lead compounds may also be present. In most applications of the polysulfide rubbers, occupational health problems are related to sensitizing contact dermatitis.

POLYURETHANE

So-called spandex fibers are polyurethane elastomers which are biologically inert. They can be substituted for rubber by persons who have become sensitized to auxiliary compounds invariably present in natural and synthetic rubbers. All spandex formulations are not identical; many are based on polytetramethylene glycol, 2,4-toluene diisocyanate, other diisocyanates, and hydrazine. The solvent for extrusion is dimethylformamide. The toxocological effects of diisocyanates are well known and constitute the principal health problem in production of these fibers.

SILICONE RUBBERS

Industrial problems have not been prominent in the preparation or use of silicone rubbers. Benzoyl peroxide may be used as a vulcanizer.

STYRENE-BUTADIENE COPOLYMER RUBBERS

Rubbers of this group are prepared in large commercial quantities for tiretreads and other similar applications. The biological properties of styrene and butadiene are significant, but from the industrial health point of view various additives have been a far greater source of difficulty.

ADDITIVES IN ELASTOMER SYSTEMS

hazards

Various substances added to rubber formulations in the course of production may be a cause of skin reaction in persons who use the finished products as well as in industrial workers. The additives are generally similar in the case of natural rubber, nitrile rubber, polybutadiene, neoprene, butyl rubber, and ethylene-propylene polymers.

Vulcanizers are generally based on elemental sulfur, although zinc and magnesium oxides are important in the neoprene cure, and peroxides are used for ethylene-propylene systems. The rate of vulcanization is influenced by accelerators, which are potent sensitizers. Common accelerators include:

benzothiazolyl disulfide
mercaptobenzothiazole (MBT)
tetraethyl thiuramdisulfide (disulfiram)
tetramethyl thiuramdisulfide (thiram)
thiocarbanilide
dithiocarbamates (zinc dimethyl, zinc diethyl, zinc dibutyl, lead dimethyl compounds)
diphenylguanidine phthalate
hexamethylene tetramine

Besides causing allergic contact dermatitis, the accelerators disulfiram and thiram can produce severe reactions when they are absorbed in conjunction with alcohol or paraldehyde. The response is related to the inhibition of the normal metabolic degradation of aldehydes, which accumulate and produce flushing, palpitations, dyspnea, nausea, and hypotension. Disulfiram of pharmaceutical grade is a drug used to produce intolerance in the therapy of alcoholism. It has been noted that cutaneous exposure to thiram will produce the alcohol effect. These reactions are due to the inhibition of aldehyde dehydrogenase, presumably through the chelation of molybdenum, and do not involve sensitization.

Inorganic accelerators such as lead oxide (litharge) may also be used.

ANTIOXIDANTS

Antioxidants are used to protect rubbers against the destructive effects of atmospheric oxygen. Those most commonly used include:

monobenzylether of hydroquinone (agerite alba)
s-di-(B-naphthyl)-p-phenylenediamine
mono and dioctyl diphenylamines
phenyl α and β naphthylamine

The monobenzyl ether of hydroquinone, in addition to being a sensitizer, is capable of producing pigment loss in many individuals, often in the absence of any previous skin reaction. This is most apparent in Negroes, in whom the response resembles vitiligo. Exposures to this compound have been sharply reduced through modifications in the rubber compounding process. Most of the amines are potent sensitizers.

Pigments and fillers include carbon black, whiting (calcium carbonate), clay, silica, and asbestos. The properties of the fibrogenic dusts are well established. There has been speculation that polycyclic aromatic carcinogens are adsorbed to carbon black particles handled in commerce, but there has been no evidence that this pigment has toxic properties.

SYNTHETIC FIBERS • 3

Polymeric textiles resemble to a great extent many of the high polymers used in plastics and elastomers. Significant chemical and physical modifications in production provide those properties which are necessary for fibers and filaments. Virgin unfinished textiles are remarkably free of biological properties.

Synthetic Textiles
- Acetates
- Acrylics (polyacrylonitrile)
- Modacrylics
- Nylon (polyamides)
- Olefin, polypropylene
- Polyester
- Rayon

ACETATES

Cellulose acetate rayons are made from wood pulp or cotton linters treated with acetic acid and acetic anhydride. Both the acid and its anhydride have a pungent odor and are potent lachrimators. The anhydride is a severe skin and eye irritant, and it may occasionally be a sensitizer. This response is presumably due to its reaction with amino groups of cutaneous protein.

potential toxicity

In the production of fibers the cellulose acetate is dissolved in a solvent for extrusion. In the case of triacetate material the solvent can be methyl acetate, glacial acetic acid, dimethylformamide, or dimethylsulfoxide. Dimethylformamide is a "universal organic solvent" which is irritating to the eyes, mucous membranes, and skin. The solvent can pass through the intact skin or can be absorbed through the lungs. Systemic intoxication is not known to have occurred in man, but evidence from animal experimentation indicates that a potential for visceral injury exists. The unpleasant fishy odor serves as a warning and tends to limit exposure. Dimethylsulfoxide has also been suggested as a vehicle for transporting other drugs through the skin. The application of this chemical to the skin generally results in erythema, itching, and burning. Wheal and erythema reactions may occur at distant sites.

For cellulose acetate (other than triacetate) the conventional solvent is acetone, a compound of very low toxicity.

ACRYLICS (POLYACRYLONITRILE)

Acrylonitrile is the chief constituent of acrylic fibers. To improve the dye and working properties of the material, acrylonitrile is frequently copolymerized with small amounts of other monomers such as acrylates, amides, vinyl esters, and various hydrocar-

bons (for example, styrene, isobutene). When the comonomer is vinyl chloride or vinylidene chloride and is present in quantities approximately equal to the acrylonitrile, the polymer is said to be a modacrylic. Modacrylics are extruded in acetone solution; acrylics are prepared for extrusion in solvents which may include dimethylformamide, dimethylsulfoxide, strong acids, and concentrated inorganic salt solutions.

NYLON

The polyamides known as nylon are used principally as fibers, to a lesser extent as resins in the plastics industry. In fiber applications nylon may be modified by titanium dioxide, a delusterant; manganese and phosphorus salts, as light stabilizers; and copper salts and acridine compounds, as heat stabilizers. These materials are not released from the finished fiber. There are no reports of ill effects among exposed workers.

POLYESTER

Fibers of this group are formed of polyethylene terephthalate. This polymer is produced from dimethyl terephthalate and ethylene glycol under the influence of catalysts which include oxides, carbonates, or acetates of the metal zinc, antimony, manganese, cobalt, calcium, or magnesium. The terephthales have few, if any, biological properties. (For Olefins, see Polyolefin Plastics, p. 339.)

RAYON

Rayon in its finished form is essentially cellulose and is without intrinsic toxicological properties. The phases of production which have been hazardous are those in which there are opportunities for exposure to carbon disulfide. In the production of rayon, wood pulp is treated with sodium hydroxide to produce alkali cellulose. This material is then reacted with carbon disulfide to produce cellulose xanthate. So-called xanthate crumb, when dissolved in dilute sodium hydroxide to form viscose, is extrudable to form rayon fibers. Modern practice is generally such that this process takes place in closed systems. Hazardous exposure is possible, however, when safe practice is ignored or if ventilation is defective. Carbon disulfide is not used in the cuprammonium process, which is used on a limited scale.

SECTION SIX

PESTICIDES

PESTICIDES • 1

It is the continuing objective of the chemical and agricultural industries to develop materials which control specific categories of pests and have minimal potential for detrimental effects in man and other desirable animal and plant species. Unfortunately this goal has not yet been achieved, and examples of clinical intoxication continue to appear, usually as the result of accidents or incorrect methods of distribution and application. The average annual death rate due to pesticides in the United States has been estimated by the Public Health Service as one per million population. Nonfatal reported poisonings approximate one per 10,000 population, or 20,000, in the country each year.

While there are literally hundreds of pesticides, their purpose, chemical structure, and toxicological properties permit agents to be classified in groups (Table 9) (Milby, 1971). Specified materials are usually not pure compounds but may be complex technical-grade mixtures which contain various isomers, by-products, and reactants. Trade-name products may include in the formulation a combination of pesticides, synergists, diluents, and other substances, all of which may have biological properties. Moreover, the composition of such formulations may change without a corresponding change in the trade name.

Table 9
Insecticides

a. Organophosphorus Compounds

Most Dangerous
- Tetraethyl pyrophosphate (TEPP)
- Phorate
- Disulfoton
- Parathion
- Demeton (systox)
- Mevinphos
- Ethyl p-nitrophenyl thionobenzene phosphonate (EPN)
- Schradan
- Methyl parathion
- Azinphosmethyl
- Dicrotophos

Dangerous
- Dichlorvos
- Diazinon
- Dioxathion
- Methyl demeton

Dimethoate
Naled
Phostex
Trichlorfon

Least Dangerous
Malathon
Ronnel

b. Chlorinated Hydrocarbon Compounds

Most Dangerous
Isobenzan
Endrin
Aldrin
Dieldrin
Toxaphene

Dangerous
Endosulfan
Dichlorodiphenyltrichloroethane (DDT)
Heptachlor
Benzene Hexachloride (BHC)
Strobane
Chlordane
Dimite
Bandane
Dicofol

Least Dangerous
Chlorbenside
Chlorobenzilate
1,1-dichloro-2,2-bis(p-chlorophenyl)ethane (TDE)
Chloropropylate
Methoxychlor

ORGANOPHOSPHORUS COMPOUNDS

Of the indicated pesticide categories, the group most commonly associated with toxic effects in man has been that which encompasses the organophosphorus compounds. Materials of this general type were originally developed as chemical warfare agents; their mechanism of action, probably in both insects and vertebrates, is based upon their inactivation of acetylcholinesterase.

biologic action

Acetylcholine (AcCh), the natural substrate of this enzyme, is a primary neurohumoral transmitter substance of the nervous system and is necessary for impulse transmission between: (1) preganglionic and postganglionic fibers of the sympathetic and parasympathetic autonomic systems; (2) postganglionic parasympathetic (cholinergic) nerves and secretory cells, smooth muscle, and cardiac muscle; (3) motor nerves and motor endplates of striated muscle; and (4) certain components of the central nervous

system. The normal transmission of an impulse by AcCh is followed by the rapid hydrolysis of the transmitter by the enzyme and limitation of the duration and intensity of the stimulus.

Organophosphorus compounds of suitable configuration, because of certain structural similarities to AcCh, become oriented to the surface of AcCh esterase molecules and undergo changes analogous to those undergone by AcCh, the natural substrate. In the case of the organophosphorus compounds, however, the bond to the enzyme is abnormally stable, and the phosphorylated enzyme loses its normal function as an AcCh esterase. AcCh consequently accumulates and causes sustained stimulation, increased function, and finally decreased function with greater accumulation.

There is a wide variation in the mammalian toxicity shown by members of this group. Certain sulfur-substituted organophosphorus compounds require metabolic oxidation before toxicity develops. Since this *in vivo* reaction occurs more rapidly in insects than in man, this chemical property is useful in increasing mammalian safety while maintaining insecticidal potency. The oxidative conversion occurs in man but is offset to a variable degree by metabolic inactivation of biologically significant portions of the insecticide molecule. As long as the inactivation processes are capable of keeping up with the activation (oxidation) processes, intoxication does not occur. The body deals effectively with small doses of parathion, an agent of this type which requires metabolic oxidation to become toxic. When the inactivation mechanism cannot handle the amount of toxic compound presented to it, symptoms occur. The balance between oxidation and inactiviation varies between individuals; it is, therefore, not surprising that variation in susceptibility to intoxication is noted.

For reasons which are not yet clearly understood phenothiazine derivatives, especially when taken over a prolonged period, may potentiate the toxicity of organophosphorus compounds (Arterberry et al., 1962). This phenomenon may be related to experimental evidence for the inhibition of cholinesterase by pharmaceutical preparations of this type. In addition neurotropic amines such as theophylline and aminophylline may have a detrimental effect. The toxicity of these materials is also influenced by exposure to ultraviolet and visible light, which may produce more potent anticholinesterase agents than the parent compound. Parathion exposed to light on plant surfaces is probably more toxic than the unirradiated insecticide (Milby et al., 1964).

Organophosphorus compounds which do not require a modification to become active are "direct" inhibitors of AcCh and

generally show high toxicity and rapid onset of systemic symptoms. They may also cause local reactions (e.g., miosis) in the absense of systemic manifestations because absorption into the body and metabolism, probably hepatic, is not necessary for activity. Compounds in this group include tetraethyl pyrophosphate (TEPP) and phosdrin, both highly toxic, and dichlorvos (DDVP), which is readily detoxified in vertebrates and consequently less hazardous.

Insecticides of the organophosphorus group can be absorbed via the lungs, skin, or gastrointestinal tract. Oral exposure is rarely of occupational origin, but accidental poisoning of children is not uncommon, especially when pesticides are improperly stored, as in soft drink bottles. Manifestations of absorption tend to occur most rapidly after respiratory exposure or after massive exposure directly to the eye. Organophosphorus insecticides are absorbed by the skin, but the rate tends to be slow except in the presence of dermatitis and high ambient temperatures. Poor hygiene, boots and gloves contaminated on the inside, and materials with severe dermal toxicity contribute to the intensity of the hazard.

clinical syndromes

The pattern of symptoms in man reflects the degree of cholinesterase inhibition and the rate at which the enzyme has become inactivated. The level of AcCh esterase can be reduced to a level as low as $\Delta 0.2$ pH/hr gradually over the course of months by repeated small doses without obvious clinical symptoms. Field experience suggests that the gradual depression of AcCh esterase by repeated low doses does not increase susceptibility to a challenge dose of insecticide. There is evidently a physiological adaptation to low enzyme levels. On the other hand, repeated doses administered prior to physiological adjustment tend to produce cumulative effects. After clinical poisoning, physiological adjustment may be assumed complete only after the blood enzyme level has returned to normal.

Moderate systemic effects of acute absorption may occur within thirty minutes after exposure via the respiratory tract, within forty-five minutes after ingestion, and within two to three hours of cutaneous exposure. Absorption from the gastrointestinal tract and skin may be prolonged. Symptoms normally reach their peak four to eight hours after onset and gradually diminish over a period as long as a week. Complete restoration of blood cholinesterase levels may require three months, depending upon degree of depression. With massive exposure or direct application of compounds to the conjunctival epithelium, the onset of symptoms is almost instantaneous, and death may follow within minutes. If the

onset of symptoms follows exposure by more than eight hours, the diagnosis of organophosphorus poisoning is open to serious question.

Clinical evidence of systemic inhibition of cholinesterase is not specific to individual compounds but is characteristic of the entire group. Systemic responses are usually heralded by the onset of effects as a result of parasympathetic stimulation which include anorexia, nausea, sweating, substernal and epigastric tightness, heartburn, and belching. A greater degree of absorption produces vomiting, hyperperistalsis with cramps and diarrhea, increased salivation and lacrimation, profuse sweating, pallor, dyspnea, and wheezing. Miosis may be observed, but it is not a constant feature, and mydriasis has been occasionally noted. Severe symptoms include involuntary defecation and urination, excessive bronchial secretions, and pulmonary edema. Evidence of inhibited cholinesterase activity at the motor endplate usually occurs after the muscarinic effects have become relatively prominent. These nicotinic phenomena include muscular twitching, fasciculation, cramps of skeletal muscle, and general weakness, especially on exertion. The muscles of respiration may be impaired.

effects on central nervous system

Central nervous system (CNS) manifestations may include anxiety, emotional aberration, insomnia or somnolence, headache, tremor, and intellectual deterioration. Electroencephalographic evidence of CNS impairment may persist for prolonged periods. The significance of these manifestations may be increased by the critical demands of certain jobs (e.g., pilot of crop-dusting aircraft). Studies of workers with chronic exposures to organophosphates have revealed neurological deficits in the absence of obvious clinical signs of intoxication (Metcalf and Holmes, 1969). Slowness of thinking, memory defects, irritability, and delayed reaction times are apparent. The chronicity and cholinesterase relationship of these clinical phenomena is not established. Death in cases of heavy exposure is usually related to respiratory collapse reflecting depression of the respiratory center, weakness of the muscles of respiration, bronchoconstriction, and excessive pulmonary secretions. Ventricular fibrillation may ensue when atropine is given in the presence of hypoxia.

local effects

Slight exposure to an aerosol of a direct inhibitor of cholinesterase may produce local physiological responses without systemic absorption. Indirect inhibitors cause poisoning only after they have been metabolized and consequently produce no local effects. Local effects upon the eye may include miosis, a sensation of retrobulbar pressure, headache, and conjunctival hyperemia.

These reactions may persist for as long as a day, and miosis has been noted to remain for five days or even longer. Localized skin responses include muscular fasciculation and circumscribed areas of sweating, developing within minutes and lasting for several hours. Respiratory exposure to an aerosol or vapor may lead to increased bronchial secretions, a sensation of chest tightness, and occasionally wheezing, with or without subsequent systemic poisoning.

delayed effects

Although the evidence is incomplete, some cholinesterase-inhibiting organophosphorus compounds can produce permanent paralysis due to a demyelinating process of the spinal cord (Bidstrup et al., 1953). This process may not become apparent for as long as a month after exposure and is similar to the chronic neurological phenomena associated with tri-o-cresylphosphate. Animal data suggest that most organophosphorus insecticides do not have this property, and demyelination in man has been attributed only to Mipafox, an agent not used in the United States.

Evidence is accumulating that renal tubular dysfunctions may be associated with absorption of organophosphorus pesticides (Davies et al., 1969). The mechanisms responsible for observed glycosuria, alterations in phosphate resorption, diminished concentrating ability, and amino acid resorption defects have not been identified. It is possible that these manifestations of toxicity are due to organophosphate metabolites such as p-nitrophenol, a known irritant which can cause dysuria.

treatment

Treatment in cases of cholinesterase inhibition is based upon the prompt administration of atropine in sufficient doses. Atropine does not influence the inactivation of cholinesterase but rather limits the exaggerated muscarinic effects of accumulated acetylcholine. Atropine has no effect upon the nicotinic manifestations of acetylcholine at the motor endplate and consequently does not influence weakness of the respiratory musculature. There is a clear danger of ventricular fibrillation in persons who receive atropine in the presence of hypoxia. While agreement on the point is not unanimous, it is the general view that the cyanotic patient should receive oxygen and artificial ventilation to correct hypoxia before atropine is administered. It is desirable to achieve a mild degree of atropine toxicity such as tachycardia, dry flushed skin, or cessation of salivary secretion, which may require unusually large doses. In severely poisoned persons, as much as 40 mg of atropine can be given in a day without producing overatropinization. A single

intravenous dose of 10 mg atropine sulfate has been inadvertently administered to normal adults with consequent obvious signs of serious overdosage but without causing a critical threat to life. The effects of intravenous atropine begin in one to four minutes and are maximal in eight minutes. The use of atropine as a prophylactic measure prior to anticipated exposure should be avoided.

Although atropine does not influence the integrity of the inactive phosphorylated enzyme complex, specific agents of the oxime type have been developed to accelerate cholinesterase reactivation. The oxime currently available in the United States is 2-pyridine aldoxime known as 2-PAM, pralidoxime chloride.* Other agents have been developed, especially in Europe. The evidence is very good that treatment with both atropine and 2-PAM is more effective than treatment with atropine alone. 2-PAM is rapidly excreted, and repeated doses may be necessary, particularly in the case of parathion and other organophosphorus compounds which must undergo bioactivation before becoming toxic. Since 2-PAM is itself a weak anticholinesterase compound, facilities for assisted ventilation should be available.

In severe cases of poisoning (coma, cyanosis) the recommended treatment should be as follows:

1. Correction of hypoxia with oxygen and assisted ventilation; removal of secretions; maintenance of patent airway.
2. Administration of atropine sulfate, 2 to 4 mg, intravenously. This should be repeated at 5- to 10-minute intervals until signs of atropine toxicity appear (dry, flushed skin; tachycardia as high as 140/min, dry mouth).
3. Administration of 2-PAM, 1 gm intravenously, slowly. The dose may be given in an infusion of 250 ml of saline over a 30-minute period. The dose can be repeated in an hour. In overwhelming exposures, the doses may be doubled.
4. Decontamination of skin and hair with soap and water, decontamination of eyes with saline. Alcohol can be used to remove final traces of material from the skin.
5. Symptomatic treatment.

In less severe cases, the following treatment is appropriate:

1. Atropine sulfate, 1 to 2 mg, if symptoms appear, repeated every 15 to 30 minutes until muscarinic symptoms are relieved or until evidence of mild atropine toxicity occurs.
2. Decontamination.
3. Administration of 2-PAM, 1 gm intravenously, slowly, if response to atropine is not satisfactory.
4. Symptomatic treatment.

*Marketed under the name Protopam chloride, Ayerst Laboratories, 3rd Avenue, New York City, N.Y.

Opiates, theophylline, aminophylline, phenothiazine, and succinylcholine are contraindicated. Seizures are generally best prevented or controlled by adequate oxygenation and the outlined regimen. Intravenous sodium thiopental can be used if necessary with extreme caution. Persons who are sufficiently ill to require atropine should remain under medical supervision for at least twenty-four hours, since absorption and bioactivation may occur for a prolonged period after the initial exposure.

prevention

Prevention of occupational exposure can be accomplished through education, care, and the use of protective clothing, respirators, and air-conditioned cabs. Careful maintenance of equipment is necessary inasmuch as boots, gloves, and overalls become readily contaminated and sources of cutaneous exposure. Spray-soaked clothing should obviously be removed promptly. Contamination of tobacco products and foods must be avoided, and the hands and face should be washed with soap and water prior to eating or smoking.

Blood analyses for cholinesterase activity are valuable in diagnosis and in medical surveillance of potentially exposed workers (Witter, 1963). Plasma cholinesterase levels drop to lower levels and recover more rapidly than do red cell cholinesterase levels which represent the true levels. Red cell cholinesterase recovers only as fast as new erythrocytes are formed, unless there has been treatment with oximes. The normal level for an individual is his pre-exposure level, and it is against this value that subsequent comparisons should be made. In the absence of pre-exposure information, group "normals" can be used, but are less satisfactory.

Colorimetric field procedures are available which permit identification of those persons whose whole blood cholinesterase activity has fallen to below 50 percent of control levels, persons who should be removed from further exposure and whose previous exposure should be examined. This method is based upon the rate of pH shift in the sample as acetylcholine is hydrolyzed with the release of acetate. A testing paper yielding relatively crude approximations of plasma cholinesterase levels is available for diagnostic field and emergency room use. Instructions for use of all field methods must be followed exactly if errors are to be avoided. Various standard laboratory methods are available for more precise enzyme determinations. Micromodifications of the Michael glass electrode pH measurement technique are most common. Normal enzyme levels have been determined by Rider et al. (1957) (in Δ pH/hr) and are in current use (1974):

Table 10
Normal Enzyme Levels

	Men	Women
Red Cells		
Range	0.39–1.02	0.34–1.10
Mean±s.d.	0.766±0.081	0.750±0.082
Plasma		
Range	0.44–1.63	0.24–1.54
Mean±s.d.	0.953±0.187	0.817±0.187

For practical purposes, a cholinesterase level of 0.5 Δ ph/Hr for either cells or plasma represents depressed activity. Also from the practical point of view, a significant reduction of cholinesterase activity can be caused only by exposure to organophosphorus or carbamate insecticides. When intoxication of at least moderate severity is suspected on clinical and epidemiological grounds, enzyme assays should be regarded as confirmatory, and treatment should not be delayed until a laboratory report is received. Symptomatic persons should not be permitted to return to work with organophosphorus compounds until cholinesterase levels have returned to 75 percent of normal. Procedures for the collection, storage, and shipment of biological materials have been fully described (Morrison and Durham, 1971). An additional surveillance method is based upon the urinary excretion levels of paranitrophenol, a metabolite of parathion and several related insecticides (Davies et al., 1966).

CARBAMATE INSECTICIDES

Insecticides of the carbamate group are becoming increasingly popular because of their efficacy and relatively low order of mammalian toxicity.

toxicity

To a large degree carbamates function in a manner similar to that associated with organophosphorus compounds—viz., there is an interference with the normal hydrolysis of acetylcholine (AcCh) by the enzyme cholinesterase. That the enzyme becomes inactive through carbamylation, the process analagous to phosphorylation, is not established. It may be that carbamates act by competition with the substrate (AcCh) for the enzyme surface rather than by forming a stable bond with the enzyme. In either case, the clinical phenomena reflecting esterase inhibition are the same. The inactivating reaction is readily reversible in the case of carbamate insecticides, and the normal enzyme can be easily regenerated. The

reversal is so rapid that measurements of blood cholinesterase in cases of poisoning are likely to be inaccurate, appearing as false negatives, unless special precautions are taken. Most carbamates are readily hydrolyzed in mammalian systems.

Most carbamates are absorbed via the lungs, skin, and gastrointestinal tract. In cases of heavy exposure, manifestations of cholinesterase inhibition may appear and resemble those of organophosphorus poisoning.

treatment

Atropine sulfate is the treatment of choice. There is disagreement as to the value of the oximes in carbamate poisoning. The best current practice would appear to avoid the use of 2-PAM in carbaryl intoxication and to regard this oxime as contraindicated.

control

In carbamate manufacturing operations and in certain commercial applications, the intensity of exposure may be evaluated by means of determinations of urinary metabolites such as 1-naphthol.

CHLORINATED HYDROCARBON INSECTICIDES

biologic action

The mechanism of action of chlorinated hydrocarbon insecticides in mammals and insects has never been clearly understood although it is apparent that these materials are neurological poisons. They are soluble in body fat, and numerous studies have been undertaken to measure the levels of chlorinated hydrocarbon insecticides in normal human tissues. Measurable concentrations of DDT and other agents have been found in normal human fat and even in neonatal tissues; however, the biological significance of these observations is unclear. The data do provide evidence that these insecticides are persistent and are absorbed by man from his foods, particularly those of animal origin. Material stored in fat is probably largely inactive, and the total amount stored in the fat of an experimental animal may be greater than the amount necessary for a single fatal dose. These agents or their metabolites may often be identified in urine or milk.

Compounds in this category may be absorbed through ingestion and via the respiratory tract. Most of them can be absorbed through the skin, and at least one, dieldrin, can be absorbed in this manner from a dry state without being in solution. Dusts containing 5 percent DDT have been applied to the skin in louse control programs for extended periods without untoward effects.

clinical signs and symptoms—diagnosis

Manifestations of central nervous system stimulation from slight exposures include headache, anorexia, nausea, and irritability. With increasing intensity of exposure weakness, paresthesias,

tremors, and muscle fibrillation may be observed. Paresthesias of the tongue, face, and lips have been noted early in the course of DDT poisoning, and in severe cases paresthesias may occur in the extremities as well. Relatively high levels of absorption accelerate the onset of these symptoms, and seizures or coma may occur. In most over-exposure situations, symptoms appear within several hours, and a delay of over eight hours would be decidedly unusual. Long-continued low-level exposures are not known to produce clinical phenomena which differ from those of the acute response to intense single exposures.

Diagnosis is based almost entirely upon the history and clinical picture. Laboratory techniques, especially gas-liquid chromatography, can identify insecticides or their metabolites in blood, urine, gastric contents, or body fat (Morrison and Durham, 1971). The correlation of these assays with the character of the illness is not very good, and it is apparent that these relatively sophisticated procedures have limited applicability in emergency situations.

treatment

Treatment is symptomatic and supportive, and no specific antidotes are available. Contaminated clothing must be removed, and material on the skin, in the hair, and under the nails must be washed away with water and soap. Emesis or gastric lavage is indicated if toxic material has been ingested. Petroleum-based solvent vehicles present the additional hazard of aspiration pneumonia; however, this is of less significance than the fact that large amounts of highly toxic material have been ingested. With severe symptoms pentobarbital sodium 0.2 to 0.5 gm may be given intravenously to control convulsions. Repeated doses may be necessary. With control of seizures, the use of phenobarbital sodium will provide more prolonged control. In severe intoxication, artificial ventilation and supplemental oxygen may be required.

Mild intoxication may be treated with oral phenobarbital alone. Symptoms of chlorinated hydrocarbon poisoning may persist as long as a week, and control of symptoms may be necessary for the entire period.

Whether or not delayed effects or chronic sequelae are related to the absorption of chlorinated hydrocarbon insecticides is not clear. Claims of a causal association with leukemia have not been supported. Aplastic anemias following exposure to lindane, the gamma isomer of benzene hexachloride (BHC) have been reported. The diagnoses are more certain than the direct cause.

OTHER INSECTICIDES

pyrethrum, rotenone, and nicotine

Pyrethrum extract is utilized in many insect sprays and powders when a rapid "knock-down" is required. Most aerosol "bombs" for home use contain pyrethrum. This material is a moderately potent skin sensitizer and cross reacts with chrysanthemum, shasta daisy, and ragweed. Systemic intoxication is not a problem. Rotenone is a similar plant derivative with properties similar to pyrethrum. Nicotine sulfate is a potent neurological poison which can be absorbed from the skin, lungs, or gastrointestinal tract.

piperonyl butoxide

Piperonyl butoxide is not an insecticide but a synergist, which permits the reduction of concentrations of pyrethrum to 10 percent of levels which would otherwise be required. This synergist is comparatively nontoxic when tested alone by conventional techniques. This and other piperonyl derivatives appear to synergize the action of a number of pesticides by inhibiting enzyme systems or preventing enzyme induction concerned with the metabolism of the primary agent. In the case of certain sulfur-containing organophosphorus insecticides, which require metabolic activation, the enzyme-inhibiting synergists are in fact antagonistic to the development of normal insecticidal potency. At the present time the applicability of these observations to the health of man is not entirely clear (Conney et al., 1972), but there is little reason to doubt that insecticidal synergists influence the metabolic detoxification of agricultural chemicals, hormones, and pharmaceuticals.

Arsenicals (e.g., Paris green lead arsenate and other inorganic compounds of arsenic are used with decreasing frequency. Hydrogen cyanide and methyl bromide are used in homes, warehouses, and ships as fumigants.

miticides

Mites, such as the red spider mite, are not insects and are not controlled by the usual insecticidal agents. Such agents, in fact, tend to kill the insect predators of mites. Nevertheless miticides (acaricides) are included in this section because they are applied in the same manner as are the insecticides and because their probable effects on man resemble those of certain insecticidal groups. The chemicals used, such as chlorbenzilate and chlorbenside, resemble the chlorinated hydrocarbon insecticides and have similar effects in animals. The mammalian toxicity of these agents is not great. Dinitrophenol and its derivatives are miticides of distinctly greater mammalian toxicity, which is outlined relative to their application as herbicides.

soil fumigants

Nematodes are not insects but inhabit the soil as do various insects, all of which are controlled by nematocidal soil fumigants.

The best known of these agents is referred to as DD, a mixture of 1,2-dichloropropane and 1,3-dichloropropene, which is an intense irritant to the eyes, skin, and mucosa of the respiratory tract. Other nematocides include methyl bromide, ethyl dibromide, and carbamates.

FUNGICIDES

The classical agricultural fungicides, sulfur and inorganic copper, have never been of great toxicological significance to man. These agents are presently being supplemented or superseded to an increasing extent by synthetic organic compounds some of which are clearly hazardous.

organomercury compounds

Among the most useful organomercurial fungicides are those based upon alkyl, alkoxyalkyl, and aryl mercury: phenyl mercury acetate, ethyl mercury phosphate, methoxyethyl mercury silicate, and a series of more complex compounds. Alkyl mercurials, which have been used as fungicidal seed dressings, are highly toxic neurological poisons capable of causing constricted visual fields, ataxia, and other widespread manifestations of central and peripheral involvement. Aryl mercury compounds are used to control fungus disease of turf, fruits, vegetables, and grain crops but not under conditions which will leave measurable residue in foods or animal feeds. The aryl, usually phenyl, derivatives are clearly less toxic; however, they can cause similar neurological disease and an active dermatitis. These materials can also be used as fungicides in paints and some leathers. Compounds of nickel, chromium, and tin may also be found in metal-based fungicides.

dithiocarbamates

Dithiocarbamate foliage sprays include a zinc compound, an iron compound, and a manganese compound. These materials are not considered to have important systemic toxicity, although they may irritate the eyes and upper airway. The material named Thiram is tetramethylthiuram disulfide, a seed protectant, also found in the rubber industry as an accelerator.

phthalimides

So-called captan and folpet, which are found in many agricultural and home garden fungicides, have not presented significant hazards to man. Both agents do have the phthalimide moiety of thalidomide and are teratogenic in the chick embryo. Present opinion, however, is that an extrapolation of this observation to man cannot be made on the basis of available evidence.

Because of unfortunate accidents associated with human consumption of seed grains that have been treated with organomercurials, hexachlorobenzene has been used as a fungicidal seed dressing. The consumption of grain prepared in this way has led to

epidemics of acquired prophyria cutanea tarda with bullous skin lesions, ulcerations, permanent pigmented scarring, and hypertrichosis (Bleibert et al., 1964; Cam and Nigogosyan, 1963). Hexachlorobenzene (C_6Cl_6) is not benzene hexachloride ($C_6H_6Cl_6$, BHC). It is an insecticide which is correctly designated as hexachlorocyclohexane.

pentachlorophenol

Pentachlorophenol is an insecticide, herbicide, and fungicide used to control weeds and the deterioration of timber. It is not applied to food crops. The action of pentachlorophenol in man is similar to that of the dinitrophenols and is based upon an uncoupling of oxidation and phosphorylation with a resultant marked increase in body temperature. Pentachlorophenol is also a potent skin and upper respiratory tract irritant.

Karathane

So-called Karathane is a member of the 4,6-dinitro-o-cresol (DNOC) dinitrophenol group and has potent fungicidal and miticidal properties. It is irritating to the eyes and upper airway but is much less toxic systemically than DNOC.

other fungicides

Other fungicidal agents used in industrial applications include creosote used as a wood preservative. Creosote can produce painful skin burns and is highly toxic on ingestion. Paranitrophenol, a methemoglobin producer, is used on leather.

HERBICIDES

Inorganic arsenicals and sodium chlorate have been used to kill weeds for many years and to sterilize soils for areas such as parking lots in which no vegetation is desired. Current usage emphasizes organic compounds, many of which are selective herbicides (i.e., agents which affect only certain types of vegetation).

chlorphenoxy group

This group includes 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), a related compound, silvex, and 2-methyl-4-chlorphenoxyacetic acid. In most applications amine salts or esters are used so as to permit control of volatility and drift. Compounds of this group act as growth-regulating hormones in plants; however, no hormonal effects are noted in animals. Skin absorption is slight, and toxicity by oral or inhalational routes has not been an agricultural health problem. Experimental and suicidal dosing has resulted in weakness, muscle twitching, myotonia, convulsions, and coma, the mechanisms for which are unknown. The group can produce a contact dermatitis and chloracne (Kimmig and Schutz, 1957), and a syndrome conforming to the description of porphyria cutanea tarda has occured in chemical operators manufacturing 2,4-D (Bleiberg et al., 1964;

Poland et al., 1971). There was associated exposure to other chemical intermediates in this situation. In each instance treatment is symptomatic.

dinitrophenols and their toxic effects

A series of substituted dinitrophenols has been prepared for use as eradicant herbicides along roadways and rights of way, as selective weed killers in fields, and as blossom thinners for fruit trees. In different formulations these compounds can be used as fungicides, miticides, and insecticides, especially as dormant sprays for the control of over-wintering insect eggs in fruit trees. Principal compounds include 4,6-dinitro-o-cresol (DNOC), 4,6-dinitro-o-sec-butylphenol, and 2,4-dinitrocyclohexylphenol. Each of these compounds, as well as others in the group, are readily absorbed by inhalation or ingestion. Most of them can be absorbed through the skin, although the cyclohexyl derivative is not absorbed in this manner to a significant degree. Compounds in this group share a common toxic mechanism whereby oxidation at the mitochondrial level is uncoupled from phosphorylation. Oxidation continues and in fact increases in response to the deficit of adenosine triphosphate.

Symptoms in man include restlessness, anxiety, flushed skin, sweating, deep and rapid respiration, tachycardia, hyperthermia, cyanosis, weakness, and coma. The increase in metabolic rate is proportional to the absorbed dose, and very high basal metabolic rates may be attained. Under such circumstances the production of heat exceeds the capacity to dissipate heat by a very great margin, and fatal hyperthermia may ensue. High ambient temperatures contribute to the disturbance of heat loss. Chronic intoxication may be marked by fatigue, unusual thirst, and weight loss as well as by symptoms of acute intoxication. There may be yellow staining of the skin from the compounds in question, although staining is not indicative of poisoning. Cataract formation may be observed and was typical of those cases arising in the 1930s from the use of dinitrophenols in weight-reducing drugs.

Laboratory findings are not usually helpful with the exception that the basal metabolic rate is elevated. Tests are available for determining blood and urine levels of dinitrophenols.

Treatment is symptomatic and based upon controlling the hyperthermia with cold baths. Oxygen and careful attention to fluid and electrolyte balance are indicated. Material on the skin should be removed with soap and water, but there is no reason to attempt to remove the fixed yellow stains of skin and hair. Atropine is absolutely contraindicated, and it is essential not to confuse the evidence for this poisoning with manifestations of cholinesterase inhibition.

Acute poisoning by the dinitrophenols usually runs a rapid course with essentially complete recovery or death within twenty-four to forty-eight hours. The excretion of these compounds is very slow, however, and persons who have shown symptoms of poisoning should be separated from risks of absorption for at least six weeks.

Those who regularly apply dinitrophenols should be checked periodically for blood levels of the compounds. Assays give a reasonably good index of the degree of absorption and the hazard to health.

carbamates, phenylureas, and triazine derivatives

Carbamate herbicides include compounds marketed under a variety of designations. The phenylurea group includes monuron, diuron, and linuron. Simazine and atrazine are of the triazine group. None of these materials has been shown to have a high level of acute mammalian toxicity, but there is evidence that the carbamates and phenylureas affect mitosis.

bipyridinium compounds and toxicity

Diquat and paraquat of the bipyridinium or quaternary ammonium group are remarkable from the toxicological point of view in that they are capable, under the proper circumstances, of causing a proliferative reaction of alveolar macrophages, alveolar cells, pulmonary fibroblasts, and terminal bronchiolar cells. This process leads to thickening and fibrosis of the alveolar walls, respiratory insufficiency, and death. In man this response has been observed only after the ingestion of a large amount of paraquat and is delayed for several days after the acute exposure (Bullivant, 1966). Renal disorders with nitrogen retention and hepatic necrosis have also been observed before the development of pulmonary fibrosis. These compounds appear to affect epithelial tissues primarily, and specific agents may attack those of the kidney or lens of the eye preferentially.

In normal field use there is no evidence that compounds of this group are injurious, but it is regarded as prudent to avoid the inhalation of mists generated in spraying.

other organic herbicides

One compound named Dalapon is based upon 2,2-dichloropropionic acid and is of no great hazard to applicators. Aminotriazole, used mainly for the destruction of poison oak and poison ivy, and the so-called Dacthal, a pre-emergent herbicide, have no prominent clinical toxicological properties.

RODENTICIDES

Inorganic rodenticides include compounds of arsenic, phosphorus, and thallium. Warfarin is a coumarin derivative and has anticoagulant properties which are familiar to physicians who use

similar preparations in clinical medicine. Single doses of warfarin do not cause important inhibition of prothrombin production, and hazards have been unusual.

Sodium fluoroacetate (Compound 1080) is an extremely toxic metabolic poison which blocks the metabolism of citrate in the tricarboxylic acid cycle. Fluoroacetate becomes incorporated into fluorocitrate, but this foreign substrate is a potent competitive inhibitor for the enzyme which normally handles citrate.

occupational hazards and therapy

Sodium fluoroacetate is readily absorbed from the gastrointestinal tract. In man the clinical response includes nausea, apprehension, epileptiform seizures, ventricular fibrillation, and death. Therapy is mainly nonspecific, although there is animal evidence that an extrinsic supply of acetate ions (via glycerol monoacetate) may be helpful. The main protection against poisoning is the limitation of use to especially qualified exterminators. This compound should not be available to householders for the control of rodents.